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(71) Anmelder *(für alle Bestimmungsstaaten mit Ausnahme von US)*: **BOEHRINGER INGELHEIM PHARMA KG** [DE/DE]; 55216 Ingelheim/Rhein (DE).

(72) Erfinder; und

(75) Erfinder/Anmelder *(nur für US)*: **ROTH, Gerald, Jürgen** [DE/DE]; Akazienweg 47, 88400 Biberach (DE). **HECKEL, Armin** [DE/DE]; Geschwister-Scholl-Strasse 71, 88400 Biberach (DE). **WALTER, Rainer** [DE/DE]; Probststrasse 3, 88400 Biberach (DE). **MEEL VAN, Jacobus** [NL/AT]; Weisses Kreuz Gasse 61, A-2340 Mödling (AT). **REDEMANN, Norbert** [DE/DE]; Köhlesrain 48, 88400 Biberach (DE). **SCHNAPP, Gisela** [DE/DE]; Esterbuch 5, 88400 Biberach (DE). **TONTSCH-GRUNT, Ulrike** [AT/AT]; Oetkerweg 23, A-2500 Baden (AT). **SPEVAK, Walter** [AT/AT]; Leoberndorferstrasse 36, A-2105 (AT).

(74) Anwalt: **LAUDIEN, Dieter**; Boehringer Ingelheim GmbH, B Patente, 55216 Ingelheim/Rhein (DE).

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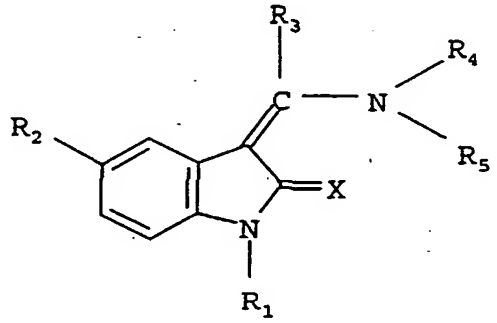
[Fortsetzung auf der nächsten Seite]

(54) Title: PRODUCTION OF 5-SUBSTITUTED INDOLINONES AND USE THEREOF AS MEDICAMENTS

(54) Bezeichnung: IN 5-STELLUNG SUBSTITUIERTE INDOLINONE, IHRE HERSTELLUNG UND IHRE VERWENDUNG ALS ARZNEIMITTEL



(I)

(57) Abstract: The invention relates to 5-substituted indolinones of general formula (I), where R^1 to R^5 and X are as defined in claim 1, the isomers and salts thereof, in particular, the physiologically acceptable salts, which exhibit valuable pharmacological properties. Said properties, in particular, include an inhibitory effect on various kinases and cyclin/CDK complexes, receptor thyrosine kinases and on the proliferation of tumour cells. The invention further relates to medicaments containing these compounds, use and methods for production thereof.

(57) Zusammenfassung: Die vorliegende Erfindung betrifft in 5-Stellung substituierte Indolinone der allgemeinen Formel (I), in der R_1 bis R_5 und X wie im Anspruch 1 definiert sind, deren Isomere und deren Salze, insbesondere deren physiologisch verträgliche Salze, welche wertvolle pharmakologische Eigenschaften aufweisen, insbesondere eine inhibierende Wirkung auf verschiedene Kinasen und Cyclin/CDK-Komplexe, auf Rezeptortyrosinkinasen sowie auf die Proliferation von Tumorzellen, diese Verbindungen enthaltende Arzneimittel, deren Verwendung und Verfahren zu ihrer Herstellung.

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Indolinones substituted in the 5 position, the preparation thereof and their use as pharmaceutical compositions

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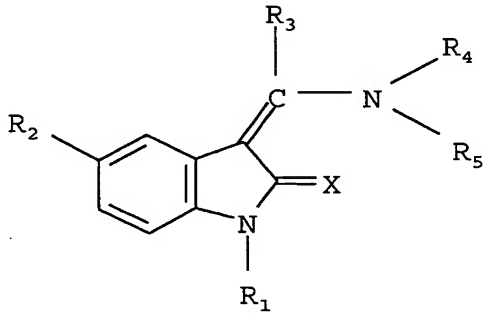
The present invention relates to new indolinones substituted in the 5 position of general formula



(I),

the isomers thereof, the salts thereof, particularly the physiologically acceptable salts thereof which have valuable properties.

The above compounds of general formula I wherein R_1 denotes a hydrogen atom or a prodrug group have valuable pharmacological properties, in particular an inhibiting effect on various kinases, especially on complexes of CDK's (CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8 and CDK9) with their specific cyclins (A, B1, B2, C, D1, D2, D3, E, F, G1, G2, H, I and K) and to viral cyclin (cf. L. Mengtao in J. Virology 71(3), 1984-1991 (1997)), to receptor tyrosine kinases such as VEGFR2, PDGFRα, PDGFRβ, FGFR1, FGFR3, EGFR, HER2, IGF1R and HGFR, and to the proliferation of cells, in particular tumour cells.

The other compounds of the above general formula I wherein R_1 does not denote a hydrogen atom or a prodrug group are

valuable intermediate products for preparing the abovementioned compounds.

The present invention thus relates to the above compounds of general formula I, whilst those compounds wherein R_1 denotes a hydrogen atom or a prodrug group have valuable pharmacological properties, pharmaceutical compositions containing the pharmacologically active compounds, the use thereof and processes for preparing them.

In the above general formula I

X denotes an oxygen or sulphur atom,

R_1 denotes a hydrogen atom or a prodrug group such as a C_{1-4}-alkoxycarbonyl or C_{2-4}-alkanoyl group,

R_2 denotes a hydroxy, C_{1-3}-alkoxy, aryloxy, phenyl-C_{1-3}-alkoxy, cyano, $(HO)_2PO$, $(HO)(C_{1-4}\text{-alkoxy})PO$, $(HO)(\text{aryloxy})PO$, $(HO)(\text{benzyloxy})PO$, $(C_{1-4}\text{-alkoxy})_2PO$, $(\text{aryloxy})_2PO$, $(\text{benzyloxy})_2PO$, $(C_{1-3}\text{-alkylenedioxy})PO$, $H(C_{1-4}\text{-alkoxy})PO$, $H(\text{aryloxy})PO$, $H(\text{benzyloxy})PO$, mercapto, C_{1-3}-alkylmercapto, arylmercapto, phenyl-C_{1-3}-alkylmercapto, C_{1-3}-alkylsulphinyl, arylsulphinyl, phenyl-C_{1-3}-alkylsulphinyl, C_{1-3}-alkylsulphonyl, arylsulphonyl, phenyl-C_{1-3}-alkylsulphonyl, sulpho, C_{1-3}-alkoxy-sulphonyl, aryloxysulphonyl, phenyl-C_{1-3}-alkoxysulphonyl, aminosulphonyl, C_{1-4}-alkylaminosulphonyl, arylaminosulphonyl, heteroarylaminosulphonyl, phenyl-C_{1-3}-alkylaminosulphonyl, di-(C_{1-4}-alkyl)-aminosulphonyl, di-(aryl)-aminosulphonyl, di-(phenyl-C_{1-3}-alkyl)-aminosulphonyl, N-(C_{1-3}-alkyl)-aryl-aminosulphonyl, N-(C_{1-3}-alkyl)-heteroarylaminosulphonyl, N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylaminosulphonyl or a 4- to 7-membered cycloalkyleneiminosulphonyl group,

R_3 denotes a hydrogen atom, a C_{1-6}-alkyl, C_{3-7}-cycloalkyl, trifluoromethyl or heteroaryl group,

a phenyl or naphthyl group, a phenyl or naphthyl group mono- or disubstituted by a fluorine, chlorine, bromine or iodine atom, by a trifluoromethyl, C_{1-3}-alkyl or C_{1-3}-alkoxy group, whilst in the event of disubstitution the substituents may be identical or different and wherein the abovementioned unsubstituted, mono- and disubstituted phenyl and naphthyl groups may additionally be substituted

by a hydroxy, hydroxy-C_{1-3}-alkyl or C_{1-3}-alkoxy-C_{1-3}-alkyl group,

by a cyano, cyano-C_{1-3}-alkyl, cyano-C_{2-3}-alkenyl, cyano-C_{2-3}-alkynyl, carboxy, carboxy-C_{1-3}-alkyl, carboxy-C_{2-3}-alkenyl, carboxy-C_{2-3}-alkynyl, C_{1-3}-alkoxycarbonyl, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkyl, C_{1-3}-alkoxycarbonyl-C_{2-3}-alkenyl or C_{1-3}-alkoxycarbonyl-C_{2-3}-alkynyl group,

by a C_{1-3}-alkylcarbonyl, C_{1-3}-alkylcarbonyl-C_{1-3}-alkyl, C_{1-3}-alkylcarbonyl-C_{2-3}-alkenyl or C_{1-3}-alkylcarbonyl-C_{2-3}-alkynyl group,

by an aminocarbonyl, aminocarbonyl-C_{1-3}-alkyl, aminocarbonyl-C_{2-3}-alkenyl, aminocarbonyl-C_{2-3}-alkynyl, C_{1-3}-alkylaminocarbonyl, C_{1-3}-alkylaminocarbonyl-C_{1-3}-alkyl, C_{1-3}-alkylaminocarbonyl-C_{2-3}-alkenyl, C_{1-3}-alkylaminocarbonyl-C_{2-3}-alkynyl, di-(C_{1-3}-alkyl)-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl-C_{1-3}-alkyl, di-(C_{1-3}-alkyl)-aminocarbonyl-C_{2-3}-alkenyl or di-(C_{1-3}-alkyl)-aminocarbonyl-C_{2-3}-alkynyl group,

by a nitro, nitro-C_{1-3}-alkyl, nitro-C_{2-3}-alkenyl or nitro-C_{2-3}-alkynyl group,

by an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl group,

by a C_{1-3}-alkylcarbonylamino, C_{1-3}-alkylcarbonylamino-C_{1-3}-alkyl, N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino-C_{1-3}-alkyl group,

by a C_{1-3}-alkylsulphonylamino, C_{1-3}-alkylsulphonylamino-C_{1-3}-alkyl, N-(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino-C_{1-3}-alkyl group,

by a C_{1-3}-alkylaminosulphonyl, C_{1-3}-alkylaminosulphonyl-C_{1-3}-alkyl, N-(C_{1-3}-alkyl)-C_{1-3}-alkylaminosulphonyl or N-(C_{1-3}-alkyl)-C_{1-3}-alkylaminosulphonyl-C_{1-3}-alkyl group,

by a cycloalkyleneimino, cycloalkyleneiminocarbonyl, cycloalkyleneiminosulphonyl, cycloalkyleneimino-C_{1-3}-alkyl, cycloalkyleneiminocarbonyl-C_{1-3}-alkyl or cycloalkyleneiminosulphonyl-C_{1-3}-alkyl group having 4 to 7 ring members in each case, wherein in each case the methylene group in the 4 position in a 6- or 7-membered cycloalkyleneimino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH or -N(C_{1-3}-alkyl) group,

or by a heteroaryl or heteroaryl-C_{1-3}-alkyl group,

R_4 denotes a phenyl group,

a phenyl group substituted by a fluorine, chlorine, bromine or iodine atom, by a cyano, nitro, C_{1-3}-alkyl or trifluoromethyl group, by a C_{1-3}-alkoxy group optionally substituted by 1 to 3 fluorine atoms, by an amino-C_{2-3}-alkoxy, C_{1-3}-alkyl-amino-C_{2-3}-alkoxy, di-(C_{1-3}-alkyl)-amino-C_{2-3}-alkoxy or benzylamino-C_{2-3}-alkoxy group, by a cycloalkyleneimino-C_{2-3}-alkoxy group having 4 to 7 ring members, by a C_{1-3}-alkylmercapto, carboxy, C_{1-3}-alkoxycarbonyl, tetrazolyl or hetero-aryl group,

a phenyl group substituted by a 4- to 7-membered cycloalkyleneimino group, wherein

a methylene group linked to the imino group may be replaced by a carbonyl or sulphonyl group or

the cycloalkylene moiety may be fused with a phenyl ring or

one or two hydrogen atoms may each be replaced by a C_{1-3}-alkyl group and/or

in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be substituted by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-C_{1-3}-alkylamino or N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH, -N(C_{1-3}-alkyl), -N(phenyl), -N(C_{1-3}-alkyl-carbonyl) or -N(benzoyl) group,

a C_{1-4}-alkylphenyl group which may be substituted in the alkyl moiety

by an amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, N-(phenyl-C_{1-4}-alkyl)-C_{1-4}-alkylamino, ω-hydroxy-C_{2-4}-alkyl-amino, di-(ω-hydroxy-C_{2-4}-alkyl)-amino or C_{3-7}-cycloalkylamino group,

by a 4- to 7-membered cycloalkyleneimino group, wherein

a methylene group linked to the imino group may be replaced by a carbonyl or sulphonyl group or

the cycloalkylene moiety may be fused to a phenyl group or to an oxazolo, imidazolo, thiazolo, pyridino, pyrazino or pyrimidino group optionally substituted by a

fluorine, chlorine, bromine or iodine atom, by a nitro, C_{1-3}-alkyl, C_{1-3}-alkoxy or amino group or

one or two hydrogen atoms in each case may be replaced by a C_{1-3}-alkyl, C_{5-7}-cycloalkyl or phenyl group and/or

in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be substituted by a hydroxy, carboxy, C_{1-4}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-C_{1-3}-alkylamino or N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH, -N(C_{1-3}-alkyl), -N(phenyl), -N(C_{1-3}-alkyl-carbonyl) or -N(benzoyl) group,

by a 5- to 7-membered cycloalkenyleneimino group, wherein the double bond is isolated from the nitrogen atom, by a phenylamino, N-(C_{1-3}-alkyl)-phenylamino, phenyl-C_{1-3}-alkyl-amino, N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino or di-(phenyl-C_{1-3}-alkyl)-amino group,

by a hydroxy, C_{1-3}-alkoxy, tetrazolyl, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, C_{1-3}-alkylcarbonyl-amino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino group or by a 4- to 7-membered cycloalkyleneiminocarbonyl group,

a phenyl group substituted by the group of formula

$$-N(R_a)-CO-(CH_2)_n-R_b \qquad (II),$$

wherein

R_a denotes a hydrogen atom or a C_{1-3}-alkyl group,

n denotes one of the numbers 0, 1, 2 or 3 and

R_b denotes an amino, C_{1-4}-alkylamino, phenylamino, N-(C_{1-4}-alkyl)-phenylamino, benzylamino, N-(C_{1-4}-alkyl)-benzylamino or di-(C_{1-4}-alkyl)-amino group, a 4- to 7-membered cycloalkyleneimino group, wherein in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH, -N(C_{1-3}-alkyl), -N(phenyl), -N(C_{1-3}-alkyl-carbonyl) or -N(benzoyl) group, or, if n denotes one of the numbers 1, 2 or 3, it also denotes a hydrogen atom,

or a phenyl group substituted by the group of formula

$$-N(R_c)-(CH_2)_m-(CO)_o-R_d \qquad (III),$$

wherein

R_c denotes a hydrogen atom, a C_{1-3}-alkyl group, a C_{1-3}-alkylcarbonyl, arylcarbonyl, phenyl-C_{1-3}-alkylcarbonyl, C_{1-3}-alkylsulphonyl, arylsulphonyl or phenyl-C_{1-3}-alkyl-sulphonyl group,

m denotes one of the numbers 1, 2, 3 or 4,

o denotes one of the numbers 0 or 1 and

R_d denotes an amino, C_{1-4}-alkylamino, phenylamino, N-(C_{1-4}-alkyl)-phenylamino, benzylamino, N-(C_{1-4}-alkyl)-benzylamino or di-(C_{1-4}-alkyl)-amino group, a 4- to 7-membered cycloalkyleneimino group, wherein the cycloalkylene moiety may be fused with a phenyl ring or in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH, -N(C_{1-3}-alkyl), -N(phenyl), -N(C_{1-3}-alkyl-carbonyl) or

-N(benzoyl) group, a C_{1-3}-alkoxy group or a di-(C_{1-4}-alkyl)-amino-C_{1-3}-alkylamino group optionally substituted in the 1 position by a C_{1-3}-alkyl group,

or, if R_3 does not denote a hydrogen atom, a C_{1-6}-alkyl, C_{3-7}-cycloalkyl or trifluoromethyl group, it may also denote an arylsulphonylaminophenyl or N-(C_{1-3}-alkyl)-arylsulphonylaminophenyl group,

wherein all the single-bonded or fused-on phenyl groups contained in the groups specified under R_4 may be mono- or disubstituted by fluorine, chlorine, bromine or iodine atoms, by C_{1-5}-alkyl, trifluoromethyl, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminosulphonyl, nitro or cyano groups, wherein the substituents may be identical or different, or two adjacent hydrogen atoms of the phenyl groups may be replaced by a methylenedioxy group,

and

R_5 denotes a hydrogen atom or a C_{1-3}-alkyl group,

wherein additionally any carboxy, amino or imino group present may be substituted by a group which can be cleaved in vivo and may thus occur in the form of a prodrug group,

and by a group which can be cleaved in vivo from an imino or amino group is meant, for example, a hydroxy group, an acyl group such as the benzoyl or pyridinoyl group or a C_{1-16}-alkanoyl group such as the formyl, acetyl, propionyl, butanoyl, pentanoyl or hexanoyl group, an allyloxycarbonyl group, a C_{1-16}-alkoxycarbonyl group such as the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert.butoxycarbonyl, pentoxycarbonyl, hexyloxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl or hexadecyloxycarbonyl group, a phenyl-C_{1-6}-alkoxycarbonyl group

such as the benzyloxycarbonyl, phenylethoxycarbonyl or phenylpropoxycarbonyl group, a C_{1-3}-alkylsulphonyl-C_{2-4}-alkoxycarbonyl, C_{1-3}-alkoxy-C_{2-4}-alkoxy-C_{2-4}-alkoxycarbonyl or R_eCO-O-(R_fCR_g)-O-CO group, wherein

R_e denotes a C_{1-8}-alkyl, C_{5-7}-cycloalkyl, phenyl or phenyl-C_{1-3}-alkyl group,

R_f denotes a hydrogen atom, a C_{1-3}-alkyl, C_{5-7}-cycloalkyl or phenyl group and

R_g denotes a hydrogen atom, a C_{1-3}-alkyl or R_eCO-O-(R_fCR_g)-O group, wherein R_e to R_g are as hereinbefore defined,

and additionally the amino group may be a phthalimido group, whilst the abovementioned ester groups may also be used as a group which can be converted in vivo into a carboxy group,

furthermore the term an aryl group denotes a phenyl or naphthyl group optionally mono- or disubstituted by a fluorine, chlorine or bromine atom or by a trifluoromethyl, C_{1-3}-alkyl, C_{1-3}-alkoxy or nitro group, and

by a heteroaryl group is meant a monocyclic 5 or 6-membered heteroaryl group optionally substituted by a C_{1-3}-alkyl group, whilst the 6-membered heteroaryl group contains one, two or three nitrogen atoms and the 5-membered heteroaryl group contains an imino group optionally substituted by a C_{1-3}-alkyl group, an oxygen or sulphur atom or an imino group optionally substituted by a C_{1-3}-alkyl group and an oxygen or sulphur atom or one or two nitrogen atoms, and moreover a phenyl ring may be fused to the abovementioned monocyclic heterocyclic groups via two adjacent carbon atoms.

Moreover, the saturated alkyl and alkoxy moieties containing more than 2 carbon atoms mentioned in the above definitions also include the branched isomers thereof such as, for

example, the isopropyl, tert.butyl, isobutyl group etc., unless otherwise stated.

Preferred compounds of the above general formula I are those wherein

X denotes an oxygen atom,

R_1 denotes a hydrogen atom, a C_{1-4}-alkoxycarbonyl or C_{2-4}-alkanoyl group,

R_2 denotes a C_{1-3}-alkoxy, C_{1-3}-alkylmercapto, C_{1-3}-alkylsulphinyl, C_{1-3}-alkylsulphonyl, cyano, $(C_{1-4}\text{-alkoxy})_2PO$, $(C_{1-3}\text{-alkylenedioxy})PO$, aminosulphonyl, C_{1-4}-alkylaminosulphonyl, di-$(C_{1-4}$-alkyl)-aminosulphonyl, phenylaminosulphonyl, N-$(C_{1-3}$-alkyl)-phenylaminosulphonyl, pyridylaminosulphonyl or N-$(C_{1-3}$-alkyl)-pyridylaminosulphonyl group, wherein the phenyl groups contained in the abovementioned groups may be mono- or disubstituted by fluorine, chlorine or bromine atoms, by C_{1-3}-alkyl, trifluoromethyl, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxy-carbonyl, aminosulphonyl, nitro or cyano groups, wherein the substituents may be identical or different,

R_3 denotes a phenyl or naphthyl group,

a phenyl or naphthyl group substituted by a fluorine, chlorine, bromine or iodine atom, by a C_{1-3}-alkyl, trifluoromethyl, hydroxy, C_{1-3}-alkoxy, nitro, cyano, amino, C_{1-3}-alkylamino, di-$(C_{1-3}$-alkyl)-amino, C_{1-3}-alkylcarbonylamino, N-$(C_{1-3}$-alkyl)-C_{1-3}-alkylcarbonylamino, C_{1-3}-alkylcarbonyl, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or di-$(C_{1-3}$-alkyl)-aminocarbonyl group,

R_4 denotes a phenyl group,

a phenyl group substituted by a fluorine, chlorine, bromine or iodine atom, by a cyano, nitro, C_{1-3}-alkyl, trifluoromethyl,

C_{1-3}-alkoxy, di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkoxy, C_{1-3}-alkylmercapto, carboxy, C_{1-3}-alkoxycarbonyl, pyrrolyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl group,

a phenyl group substituted by a 5- to 7-membered cycloalkyleneimino group, wherein

a methylene group linked to the imino group may be replaced by a carbonyl or sulphonyl group or

the cycloalkylene moiety may be fused with a phenyl ring or

one or two hydrogen atoms may be replaced in each case by a C_{1-3}-alkyl group and/or

in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be substituted by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH or -N(C_{1-3}-alkyl) group,

a C_{1-4}-n-alkylphenyl group which may be terminally substituted in the alkyl moiety

by an amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, N-(phenyl-C_{1-2}-alkyl)-C_{1-4}-alkylamino, 2-hydroxyethyl-amino, di-(2-hydroxyethyl)-amino or C_{5-6}-cycloalkyl-amino group,

by a 5- to 7-membered cycloalkyleneimino group, wherein

one or two hydrogen atoms in each case may be replaced by a C_{1-3}-alkyl group or

the methylene group in the 4 position of a piperidino group may be substituted by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group or

the cycloalkylene moiety may be fused to a phenyl group or to an imidazolo or pyridino group optionally substituted by a fluorine, chlorine or bromine atom or by a C_{1-3}-alkyl or C_{1-3}-alkoxy group or

may be replaced by an oxygen or sulphur atom or by a sulphinyl, sulphonyl, -NH or -N(C_{1-3}-alkyl) group,

by a 3-pyrrolin-1-yl or 3,4-dehydropiperidino group, by a phenylamino, N-(C_{1-3}-alkyl)-phenyl-amino, phenyl-C_{1-3}-alkylamino, N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino or di-(phenyl-C_{1-3}-alkyl)-amino group,

by an aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, C_{1-3}-alkylcarbonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino group,

a phenyl group substituted by the group of formula

$$-N(R_a)-CO-(CH_2)_n-R_b \qquad (II),$$

wherein

R_a denotes a hydrogen atom or a C_{1-3}-alkyl group,

n denotes one of the numbers 0, 1 or 2 and

R_b denotes an amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, phenylamino or benzylamino group or a 5- to 6-membered cycloalkyleneimino group, wherein the methylene group in the 4 position of the piperidino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH

or -N(C_{1-3}-alkyl) group, or, if n denotes the number 1 or 2, it may also represent a hydrogen atom,

or a phenyl group substituted by the group of formula

$$-N(R_c)-(CH_2)_m-(CO)_o-R_d \qquad (III),$$

wherein

R_c denotes a hydrogen atom, a C_{1-3}-alkyl, C_{1-3}-alkylcarbonyl or C_{1-3}-alkylsulphonyl group,

m denotes one of the numbers 1, 2 or 3,

o denotes one of the numbers 0 or 1 and

R_d denotes an amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, phenylamino or benzylamino group or a 5- to 6-membered cycloalkyleneimino group, wherein the methylene group in the 4 position of the piperidino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH or -N(C_{1-3}-alkyl) group, a di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl-amino group optionally substituted in the 1 position by a C_{1-3}-alkyl group or, if n denotes the number 1 or 2, it may also represent a hydrogen atom,

or a phenylsulphonylaminophenyl or N-(C_{1-3}-alkyl)-phenylsulphonylaminophenyl group,

wherein all the single-bonded or fused-on phenyl groups contained in the groups specified under R_4 may be mono- or disubstituted by fluorine, chlorine or bromine atoms, by C_{1-3}-alkyl, trifluoromethyl, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminosulphonyl, nitro or cyano groups, wherein the substituents may be identical or different, or two adjacent hydrogen atoms of the phenyl groups may be replaced by a methylenedioxy group, and

R_5 denotes a hydrogen atom or a methyl group,

the isomers and the salts thereof.

Particularly preferred compounds of the above general formula I are those wherein

X denotes an oxygen atom,

R_1 denotes a hydrogen atom, a C_{1-4}-alkoxycarbonyl or C_{2-4}-alkanoyl group,

R_2 denotes a C_{1-3}-alkoxy, C_{1-3}-alkylmercapto, C_{1-3}-alkylsulphinyl, C_{1-3}-alkylsulphonyl, cyano, $(C_{1-4}\text{-alkoxy})_2PO$, aminosulphonyl, C_{1-4}-alkylaminosulphonyl, di-(C_{1-4}-alkyl)-aminosulphonyl, phenylaminosulphonyl, N-(C_{1-3}-alkyl)-phenylaminosulphonyl, 3-pyridylaminosulphonyl or N-(C_{1-3}-alkyl)-3-pyridylaminosulphonyl group, wherein the phenyl groups contained in the abovementioned groups may be substituted by a fluorine, chlorine or bromine atom, a C_{1-3}-alkyl, trifluoromethyl, C_{1-3}-alkoxy, nitro or cyano group,

R_3 denotes a phenyl or naphthyl group, but particularly the phenyl group,

R_4 denotes a phenyl group,

a phenyl group substituted by a fluorine, chlorine, bromine or iodine atom, by a cyano, nitro, C_{1-3}-alkyl, trifluoromethyl, C_{1-3}-alkoxy, di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkoxy, C_{1-3}-alkylmercapto, carboxy, C_{1-3}-alkoxycarbonyl, pyridinyl or imidazolyl group,

a phenyl group substituted by a pyrrolidino, piperidino, 2,6-dimethyl-piperidino, 3,5-dimethyl-piperidino or azepino group, wherein

the methylene group in the 4 position of the piperidino group may be substituted by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH or -N(C_{1-3}-alkyl) group,

a C_{1-3}-n-alkylphenyl group which may be terminally substituted in the alkyl moiety

by an amino, C_{1-4}-alkylamino or di-(C_{1-4}-alkyl)-amino group,

by a N-(phenylmethyl)-C_{1-4}-alkylamino group which may be monosubstituted in the phenyl moiety by a fluorine, chlorine or bromine atom, a C_{1-3}-alkyl, C_{1-3}-alkoxy, trifluoromethyl or cyano group or disubstituted by two C_{1-3}-alkyl or C_{1-3}-alkoxy groups,

by a 2-hydroxyethyl-amino, di-(2-hydroxyethyl)-amino, cyclopentylamino or cyclohexylamino group,

by a pyrrolidino, piperidino, 2,6-dimethyl-piperidino, 3,5-dimethyl-piperidino or cyclohexyleneimino group, wherein

the methylene group in the 4 position of the piperidino group may be substituted by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH or -N(C_{1-3}-alkyl) group,

or the cycloalkylene moiety may be fused to a phenyl group,

by a 3-pyrrolin-1-yl or 3,4-dehydropiperidino group, by a phenylamino, N-(C_{1-3}-alkyl)-phenylamino, phenyl-C_{1-3}-alkylamino, N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkyl-amino or di-(phenyl-C_{1-3}-alkyl)-amino group,

by an aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, C_{1-3}-alkylcarbonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino group,

a phenyl group substituted by the group of formula

$$-N(R_a)-CO-(CH_2)_n-R_b \qquad (II),$$

wherein

R_a denotes a C_{1-3}-alkyl group,

n denotes one of the numbers 0, 1 or 2 and

R_b denotes an amino, C_{1-3}-alkylamino, di-(C_{1-4}-alkyl)-amino, pyrrolidino or piperidino group, wherein the methylene group in the 4 position of the piperidino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH or -N(C_{1-3}-alkyl) group,

or a phenyl group substituted by the group of formula

$$-N(R_c)-(CH_2)_m-(CO)_o-R_d \qquad (III),$$

wherein

R_c denotes a C_{1-3}-alkylcarbonyl or C_{1-3}-alkylsulphonyl group,

m denotes one of the numbers 1, 2 or 3,

o denotes one of the numbers 0 or 1 and

R_d denotes an amino, C_{1-3}-alkylamino, di-(C_{1-4}-alkyl)-amino, pyrrolidino or piperidino group, wherein the methylene group in the 4 position of the piperidino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH or -N(C_{1-3}-alkyl) group, or a di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkylamino group optionally substituted in the 1 position by a C_{1-3}-alkyl group,

or a phenylsulphonylaminophenyl or N-(C_{1-3}-alkyl)-phenylsulphonylaminophenyl group,

wherein all the single-bonded or fused-on phenyl groups contained in the groups specified under R_4 may be substituted by a fluorine, chlorine or bromine atom, by a methyl, trifluoromethyl, methoxy, carboxy, methoxy-carbonyl, ethoxycarbonyl, aminosulphonyl, nitro or cyano group, or two adjacent hydrogen atoms of the phenyl groups may be replaced by methoxy groups or by a methylenedioxy group, and

R_5 denotes a hydrogen atom,

the isomers and the salts thereof.

The following are mentioned as examples of particularly preferred compounds:

(a) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-methylsulphinyl-2-indolinone,

(b) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-methylsulphonyl-2-indolinone,

(c) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-(N-methyl-N-phenyl-aminosulphonyl)-2-indolinone,

(d) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-(N-butyl-N-methyl-aminosulphonyl)-2-indolinone,

(e) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-(phenylaminosulphonyl)-2-indolinone,

(f) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone,

(g) 3-Z-[1-(4-((N-benzyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone,

(h) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone,

(i) 3-Z-[1-(4-(N-(dimethylaminocarbonyl-methyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone,

(j) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone,

(k) 3-Z-[1-(4-(2-dimethylamino-ethyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone,

(l) 3-Z-[1-(4-(dimethylamino-methyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone,

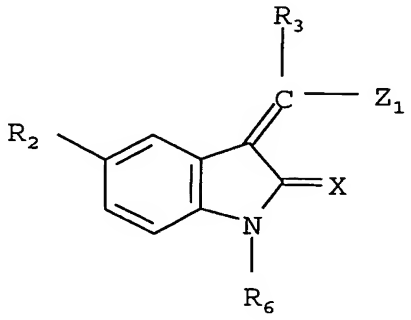
(m) 3-Z-[1-(4-(N-methyl-acetylamino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone and

(n) 3-Z-[1-(4-(N-methyl-piperazin-1-yl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

and the isomers and the salts thereof.

According to the invention, the new compounds may be obtained, for example, by the following methods known in principle from the literature:

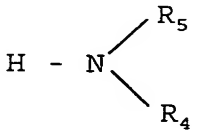
a. reaction of a compound of general formula



(IV),

wherein
X, R_2 and R_3 are as hereinbefore defined and
R_6 denotes a hydrogen atom or a protecting group for the nitrogen atom of the lactam group, wherein R_6 may also denote a bond to a solid phase optionally formed via a spacer, and
Z_1 denotes a halogen atom, a hydroxy, alkoxy or aryloxy group, e.g. a chlorine or bromine atom, a methoxy, ethoxy or benzyloxy group,

with an amine of general formula



(III),

wherein
R_4 and R_5 are as hereinbefore defined,
and if necessary subsequently cleaving any protecting group used for the nitrogen atom of the lactam group or cleaving from a solid phase.

A protecting group for the nitrogen atom of the lactam group might be for example an acetyl, benzoyl, ethoxycarbonyl, tert.butyloxycarbonyl or benzyloxycarbonyl group and

The solid phase might be a resin such as a 4-(2',4'-dimethoxyphenylaminomethyl)-phenoxy resin, wherein the bond may conveniently be formed via the amino group, or a p- benzyloxybenzylalcohol resin, wherein the bond may conveniently be formed via an intermediate member such as a 2,5-dimethoxy-4-hydroxy-benzyl derivative.

The reaction is conveniently carried out in a solvent such as dimethylformamide, toluene, acetonitrile, tetrahydrofuran, dimethylsulphoxide, methylene chloride or mixtures thereof, optionally in the presence of an inert base such as triethylamine, N-ethyl-diisopropylamine or sodium hydrogen carbonate at temperatures between 20 and 175°C, whilst any protecting group used can be cleaved simultaneously by transamidation.

If Z_1 in a compound of general formula II denotes a halogen atom, the reaction is preferably carried out in the presence of an inert base at temperatures between 20 and 120°C.

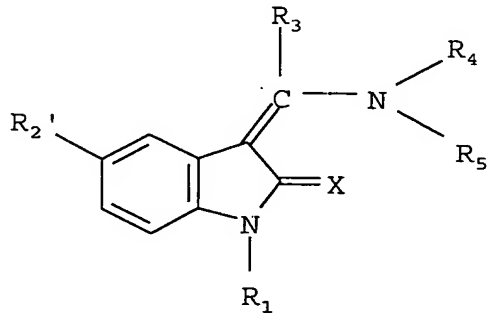
If Z_1 in a compound of general formula II denotes a hydroxy, alkoxy or aryloxy group, the reaction is preferably carried out at temperatures between 20 and 200°C.

If any protecting group used subsequently has to be cleaved, this is conveniently carried out either hydrolytically in an aqueous or alcoholic solvent, e.g. in methanol/water, ethanol/water, isopropanol/water, tetrahydrofuran/water, dioxane/water, dimethylformamide/water, methanol or ethanol in the presence of an alkali metal base such as lithium hydroxide, sodium hydroxide or potassium hydroxide at temperatures between 0 and 100°C, preferably at temperatures between 10 and 50°C,

or advantageously by transamidation with an organic base such as ammonia, butylamine, dimethylamine or piperidine in a solvent such as methanol, ethanol, dimethylformamide and mixtures thereof or in an excess of the amine used at temperatures between 0 and 100°C, preferably at temperatures between 10 and 50°C.
Any solid phase used is preferably cleaved using trifluoroacetic acid and water at temperatures between 0 and 35°C, preferably at ambient temperature.

b. In order to prepare a compound of general formula I wherein R_2 denotes one of the abovementioned substituted sulphinyl or sulphonyl groups:

oxidation of a compound of general formula



(VI),

wherein
R_1 and R_3 to R_5 are as hereinbefore defined and
R_2' denotes one of the substituted mercapto or sulphinyl groups mentioned for R_2 hereinbefore.
The oxidation is preferably carried out in a solvent or mixture of solvents, e.g. in water, water/pyridine, acetone, methylene chloride, acetic acid, acetic acid/acetic anhydride, dilute sulphuric acid or trifluoroacetic acid, expediently at temperatures between -80 and 100°C, depending on the oxidising agent used.

In order to prepare a corresponding sulphinyl compound of general formula I the oxidation is expediently carried out with one equivalent of the oxidising agent used, e.g. with hydrogen peroxide in glacial acetic acid, trifluoroacetic acid or formic acid at 0 to 20°C or in acetone at 0 to 60°C, with a peracid such as performic acid in glacial acetic acid or trifluoroacetic acid at 0 to 50°C or with m-chloroperbenzoic acid in methylene chloride, chloroform or dioxane at -20 to 80°C, with sodium metaperiodate in aqueous methanol or ethanol at -15 to 25°C, with bromine in glacial acetic acid or aqueous acetic acid optionally in the presence of a weak base such as sodium acetate, with N-bromosuccinimide in ethanol, with tert.butylhypochlorite in methanol at -80 to -30°C, with iodobenzodichloride in aqueous pyridine at 0 to 50°C, with nitric acid in glacial acetic acid at 0 to 20°C, with chromic acid in glacial acetic acid or in acetone at 0 to 20°C and with sulphuryl chloride in methylene chloride at -70°C, the resulting thioether-chlorine complex is expediently hydrolysed with aqueous ethanol.

In order to prepare a sulphonyl compound of general formula I the oxidation is expediently carried out starting from a corresponding sulphinyl compound with one or more equivalents of the oxidising agent used or starting from a corresponding mercapto compound, expediently with two or more equivalents of the oxidising agent used, e.g. with hydrogen peroxide in glacial acetic acid/acetic anhydride, trifluoroacetic acid or in formic acid at 20 to 100°C or in acetone at 0 to 60°C, with a peracid such as performic acid or m-chloroperbenzoic acid in glacial acetic acid, trifluoroacetic acid, methylene chloride or chloroform at temperatures between 0 and 60°C, with nitric acid in glacial acetic acid at 0 to 20°C, with chromic acid, sodium periodate or potassium permanganate in acetic acid, water/sulphuric acid or in acetone at 0 to 20°C.

If according to the invention a compound of general formula I is obtained which contains an alkoxycarbonyl group, this can

be converted by hydrolysis into a corresponding carboxy compound, or

If a compound of general formula I is obtained which contains an amino or alkylamino group, this may be converted by alkylation or reductive alkylation into a corresponding alkylamino, dialkylamino or pyrrolidino compound, or

If a compound of general formula I is obtained which contains an amino or alkylamino group, this may be converted by acylation into a corresponding acyl compound, or

If a compound of general formula I is obtained which contains a carboxy group, this may be converted by esterification or amidation into a corresponding ester or aminocarbonyl compound, or

If a compound of general formula I is obtained which contains a nitro group, this can be converted by reduction into a corresponding amino compound.

The subsequent hydrolysis is preferably carried out in an aqueous solvent, e.g. in water, methanol/water, ethanol/water, isopropanol/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as lithium hydroxide, sodium hydroxide or potassium hydroxide at temperatures between 0 and 100°C, preferably at temperatures between 10 and 50°C.

The subsequent reductive alkylation is preferably carried out in a suitable solvent such as methanol, methanol/water, methanol/water/ammonia, ethanol, ether, tetrahydrofuran, dioxane or dimethylformamide, optionally with the addition of an acid such as hydrochloric acid in the presence of catalytically activated hydrogen, e.g. hydrogen in the presence of Raney nickel, platinum or palladium/charcoal, or

in the presence of a metal hydride such as sodium borohydride, sodium cyanoborohydride, lithium borohydride or lithium aluminium hydride at temperatures between 0 and 100°C, preferably at temperatures between 20 and 80°C.

The subsequent acylation is preferably carried out in a solvent such as methylene chloride, diethylether, tetrahydrofuran, toluene, dioxane, acetonitrile, dimethylsulphoxide or dimethylformamide, optionally in the presence of an inorganic or a tertiary organic base, preferably at temperatures between 20°C and the boiling temperature of the solvent used. The acylation with a corresponding acid is preferably carried out in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, tetraethyl orthocarbonate, trimethyl orthoacetate, 2,2-dimethoxypropane, tetramethoxysilane, thionylchloride, trimethylchlorosilane, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexyl-carbodiimide/N-hydroxysuccinimide, N,N'-dicyclohexylcarbodiimide/1-hydroxy-benztriazole, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate/1-hydroxy-benzotriazole, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, and optionally with the addition of a base such as pyridine, 4-dimethylamino-pyridine, N-methyl-morpholine or triethylamine, conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 100°C, and the acylation with a corresponding reactive compound such as an anhydride, ester, imidazolide or halide thereof is optionally carried out in the presence of a tertiary organic base such as triethylamine, N-ethyl-diisopropylamine, N-methyl-morpholine or pyridine at temperatures between 0 and 150°C, preferably at temperatures between 50 and 100°C.

The subsequent esterification or amidation is expediently carried out by reacting a corresponding reactive carboxylic

acid derivative with a corresponding alcohol or amine as described hereinbefore.

The subsequent reduction of a nitro group is preferably carried out by hydrogenolysis, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal or Raney nickel in a solvent such as methanol, ethanol, ethyl acetate, dimethylformamide, dimethylformamide/acetone or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid or glacial acetic acid at temperatures of between 0 and 50°C, but preferably at ambient temperature, and at a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar.
In the reactions described hereinbefore, any reactive groups present such as carboxy, aminosulphonyl, amino, alkylamino or imino groups may be protected during the reaction by conventional protecting groups which are cleaved again after the reaction.

For example, a protecting group for a carboxyl group may be a trimethylsilyl, methyl, ethyl, tert.butyl, benzyl or tetrahydropyranyl group and

protecting groups for an amino, alkylamino or imino group may be an acetyl, trifluoroacetyl, benzoyl, ethoxycarbonyl, tert.butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl or 2,4-dimethoxybenzyl group and additionally, for the amino group, a phthalyl group.

Any protecting group used is optionally subsequently cleaved for example by hydrolysis in an aqueous solvent, e.g. in water, isopropanol/water, tetrahydrofuran/water or dioxane/water, in the presence of a acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as lithium hydroxide, sodium hydroxide or potassium hydroxide, at temperatures between 0 and 100°C, preferably at temperatures between 10 and 50°C.

However, a benzyl, methoxybenzyl or benzyloxycarbonyl group is cleaved, for example, hydrogenolytically, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal in a solvent such as methanol, ethanol, ethyl acetate, dimethylformamide, dimethylformamide/acetone or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid or glacial acetic acid at temperatures between 0 and 50°C, but preferably at ambient temperature, and at a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar.

A methoxybenzyl group may also be cleaved in the presence of an oxidising agent such as cerium(IV)ammonium nitrate in a solvent such as methylene chloride, acetonitrile or acetonitrile/water at temperatures of between 0 and 50°C, but preferably at ambient temperature.

A 2,4-dimethoxybenzyl group, however, is preferably cleaved in trifluoroacetic acid in the presence of anisol.

A tert.butyl or tert.butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid or hydrochloric acid, optionally using a solvent such as methylene chloride, dioxane, ethyl acetate or ether.

A phthalyl group is preferably cleaved in the presence of hydrazine or a primary amine such as methylamine, ethylamine or n-butylamine in a solvent such as methanol, ethanol, isopropanol, toluene/water or dioxane at temperatures between 20 and 50°C.

Moreover, chiral compounds of general formula I obtained may be resolved into their enantiomers and/or diastereomers.

Thus, for example, the compounds of general formula I obtained which occur as racemates may be separated by methods known *per*

se (cf. Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of general formula I with at least 2 asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known *per se*, e.g. by chromatography and/or fractional crystallisation, and, if these compounds are obtained in racemic form, they may subsequently be resolved into the enantiomers as mentioned above.

The enantiomers are preferably separated by column separation on chiral phases or by recrystallisation from an optically active solvent or by reacting with an optically active substance which forms salts or derivatives such as e.g. esters or amides with the racemic compound, particularly acids and the activated derivatives or alcohols thereof, and separating the diastereomeric mixture of salts or derivatives thus obtained, e.g. on the basis of their differences in solubility, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Optically active acids in common use are e.g. the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolyltartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, N-acetylglutamic acid, aspartic acid, N-acetylaspartic acid or quinic acid. An optically active alcohol may be for example (+)- or (-)-menthol and an optically active acyl group in amides, for example, may be a (+)- or (-)-menthyloxycarbonyl group.

Furthermore, the compounds of formula I obtained may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts with inorganic or organic acids. Acids which may be used for this purpose include for example hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid, maleic acid or methanesulphonic acid.

Moreover, if the new compounds of formula I thus obtained contain a carboxy group, they may subsequently, if desired, be converted into the salts thereof with inorganic or organic bases, particularly for pharmaceutical use into the physiologically acceptable salts thereof. Suitable bases for this purpose include for example sodium hydroxide, potassium hydroxide, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

The compounds of general formulae IV to VI used as starting materials are known from the literature in some cases or may be obtained by methods known from the literature or may be obtained by the methods described hereinbefore and in the Examples. For example, the compounds of general formula VI are described in German Patent Application 198 24 922.5.

As already mentioned, the new compounds of general formula I wherein R_4 denotes a hydrogen atom or a prodrug group have valuable pharmacological properties, particularly inhibitory effects on various kinases and cyclin/CDK complexes, on the proliferation of cultivated human tumour cells and, when administered orally, on the growth of tumours in naked mice which have been infected with human tumour cells.

For example, the compounds listed in Table 1 were tested for their biological properties as follows:

Test 1

Inhibition of cyclin/CDK enzyme, activity *in vitro*

High Five™ insect cells (BTI-TN-5B1-4) which were infected with a high titre of recombinant Baculovirus were used for the production of active human cyclin/CDK holoenzymes. By using a Baculovirus vector containing two promoters (polyhedrin enhancer promoter, P10-enhancer promoter), GST-tagged cyclins (e.g. cyclin D1 or cyclin D3) were expressed in the same cell

with the corresponding His_6-tagged CDK subunit (e.g. for CDK4 or CDK6). The active holoenzyme was isolated by affinity chromatography on glutathione-sepharose. Recombinant GST-tagged pRB (aa 379-928) was produced in E. coli and purified by affinity chromatography on glutathione-sepharose.

The substrates used for the kinase assays depended on the specific kinases. Histone H1 (Sigma) was used as the substrate for cyclin E/CDK2, cyclin A/CDK2, cyclin B/CDK1 and for v-cyclin/CDK6. GST-tagged pRB (aa 379-928) was used as the substrate for cyclin D1/CDK4, cyclin D3/CDK4, cyclin D1/CDK6 and for cyclin D3/CDK6.

Lysates of the insect cells infected with recombinant Baculovirus or recombinant kinases (obtained from the lysates by purification) were incubated together with radiolabelled ATP in the presence of a suitable substrate with various concentrations of the inhibitor in a 1% DMSO solution (dimethylsulphoxide) for 45 minutes at 30°C. The substrate proteins with associated radioactivity were precipitated with 5% TCA (trichloroacetic acid) in hydrophobic PVDF multi-well microtitre plates (Millipore) or with 0.5% phosphoric acid solution on Whatman P81 filters. After the addition of scintillation liquid the radioactivity was measured in a Wallace 1450 Microbeta Liquid Scintillation Counter. Dual measurements were taken for each concentration of the substance; IC_{50} values for the enzyme inhibition were calculated.

Test 2

Inhibition of the proliferation of cultivated human tumour cells

Cells of the Leiomyosarcoma tumour cell line SK-UT-1B (obtained from the American Type Culture Collection (ATCC)) were cultivated in Minimum Essential Medium with non-essential amino acids (Gibco), supplemented with sodium pyruvate (1

mMol), glutamine (2 mMol) and 10% foetal calf serum (Gibco) and harvested in the logarithmic growth phase. Then the SK-UT-1B cells were placed in Cytostar® multi-well plates (Amersham) at a density of 4000 cells per well and incubated overnight in an incubator. Various concentrations of the compounds (dissolved in DMSO; final concentration: <1%) were added to the cells. After 48 hours' incubation, ^{14}C-thymidine (Amersham) was added to each well and incubation was continued for a further 24 hours. The quantity of ^{14}C-thymidine which was incorporated into the tumour cells in the presence of the inhibitor and which represents the number of cells in the S phase was measured in a Wallace 1450 Microbeta Liquid Scintillation Counter. IC_{50} values for the inhibition of the proliferation (= inhibition of incorporated ^{14}C-thymidine) were calculated, correcting for the background radiation. All the measurements were done twice.

The following Table 1 contains the results of *in vitro* Test 2:

Compound (Example No.)	Inhibition of SKUT-1B-proliferation IC_{50} [μM]
3	0.0090
3(1)	0.0300
1(12)	0.0016
1(13)	0.0050
1(11)	0.0009
1(3)	0.0180
1(4)	0.0150
1(7)	0.0093
1(8)	0.0850
1(9)	0.0110
1(14)	0.0010
1(15)	0.0010
1(22)	0.0040
1(23)	0.0010

In view of their biological properties the new compounds of general formula I, the isomers and the physiologically acceptable salts thereof are suitable for treating diseases characterised by excessive or anomalous cell proliferation.

Such diseases include (with no claim to completeness): viral infections (e.g. HIV and Kaposi's sarcoma); inflammation and autoimmune diseases (e.g. colitis, arthritis, Alzheimer's disease, glomerulonephritis and wound healing); bacterial, fungal and/or parasitic infections; leukaemias, lymphoma and solid tumours; skin diseases (e.g. psoriasis); bone diseases; cardiovascular diseases (e.g. restenosis and hypertrophism). They are also useful in protecting proliferating cells (e.g. hair, intestinal, blood and progenitor cells) from damage to

the DNA caused by radiation, UV treatment and/or cytostatic treatment.

The new compounds may be used for short or long term treatment of the abovementioned diseases, optionally in conjunction with other "state-of-the-art" compounds, such as other cytostatics.

The dosage required to achieve such an effect is conveniently 0.1 to 30 mg/kg, preferably 0.3 to 10 mg/kg, by intravenous route and 0.1 to 100 mg/kg, preferably 0.3 to 30 mg/kg, by oral route, 1 to 4 times a day in each case.
For this purpose the compounds of formula I prepared according to the invention may be formulated, optionally in conjunction with other active substances, together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethyleneglycol, propyleneglycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, to form conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions, suppositories or as solutions for injections or infusions.

The following Examples are intended to illustrate the present invention:

Preparation of the starting compounds:

Abbreviations used:

TBTU = O-(benzotriazol-1-yl)-N,N,N',N'-bis(tetramethylene)-uronium hexafluorophosphate
HOBt = 1-hydroxy-1H-benzotriazole

Example A

tert.butyl (5-methylmercapto-2-nitro-phenyl)-acetate

6.4 g of potassium-tert.butoxide are placed in 120 ml of dimethylformamide and at 5°C a mixture of 4.1 g of 4-methylmercapto-nitrobenzene and 3.8 g of tert.butyl 2-chloro-acetate are rapidly added dropwise to 20 ml of dimethylformamide. The resulting solution is stirred for a further 8 minutes and then poured onto a mixture of 1.6 l of ice-cooled water and 100 ml of concentrated hydrochloric acid. The solution is extracted five times with 150 ml of methylene chloride, the combined organic phases were washed twice with 200 ml of water, dried over sodium sulphate and evaporated down. The residue is purified through a silica gel column with methylene chloride/cyclohexane (7:3) as eluant.
Yield: 2.7 g of (39 % of theory),
R_f value: 0.45 (silica gel, methylene chloride/cyclohexane = 7:3)
$C_{13}H_{17}NO_4S$
mass spectrum: m/z = 283 [M^+]

Example B

5-methylmercapto-2-indolinone

2.7 g of tert.butyl (5-methylmercapto-2-nitro-phenyl)-acetate are dissolved in 10.4 ml of glacial acetic acid and 3.7 ml of

concentrated hydrochloric acid and 3.7 g of tin(II)-chloride dihydrate are added. The mixture is stirred for 5 hours at 110°C. After cooling the solvent is eliminated, the residue is mixed with 100 ml of ice-water and made basic with sodium hydroxide solution. The aqueous phase is extracted with methylene chloride and the organic phase is dried over sodium sulphate. After elimination of the solvent the product is recrystallised from petroleum ether.
Yield: 2.3 g of (61 % of theory),
R_f value: 0.12 (silica gel, methylene chloride)
C_9H_9NOS
Melting point: 112-114°C

Example C

5-Diethoxyphosphoryl-2-indolinone
3.0 g of 5-Bromo-2-indolinone (prepared according to J. Med. Chem. 41, 2588 (1998)), 3.6 ml of diethyl phosphite and 3.9 ml of triethylamine are dissolved in 20 ml of absolute toluene. Then 0.8 g of tetrakistriphenylphosphine palladium(0) are added and the mixture is stirred for 30 hours at 90°C. After 20 hours another 10 ml of absolute toluene, 3.0 ml of diethyl phosphite, 3.0 ml of triethylamine and 0.7 g of tetrakistriphenylphosphine palladium(0) are added. After the end of the reaction time the mixture is filtered over kieselguhr and the filtrate is concentrated by evaporation. The residue is purified through a silica gel column with ethyl acetate, then with ethyl acetate/ethanol (10:1). The product is recrystallised from ether and dried *in vacuo* at 100°C.
Yield: 2.3 g (61 % of theory),
R_f value: 0.4 (silica gel, ethyl acetate/ethanol = 10:1)
$C_{12}H_{16}NO_4P$
ESI-mass spectrum: m/z = 268 $[M-H^-]$

Example D

5-Chlorosulphonyl-2-indolinone

To 25.0 ml of chlorosulphonic acid are added 10.0 g of 2-indolinone at -10°C to 0°C in small batches. The mixture is stirred overnight at room temperature, poured onto 600 ml of ice-water (violent reaction) and stirred for 1 hour. The white precipitate formed is suction filtered, washed thoroughly with water and dried for 3 hours at 70°C.

Yield: 14.3 g of (82 % of theory),

R_f value: 0.48 (silica gel, methylene chloride/methanol = 9:1)

$C_8H_6ClNO_3S$

ESI-mass spectrum: m/z = 230/232 $[M-H^-]$

Example E

5-aminosulphonyl-2-indolinone

2.0 g of 5-chlorosulphonyl-2-indolinone are suspended in 40 ml of methylene chloride, combined with 10 ml of aqueous ammonia and stirred for 3 hours at room temperature. The precipitate formed is filtered off and washed with ether.

Yield: 1.0 g of (55 % of theory),

R_f value: 0.14 (silica gel, methylene chloride/methanol = 9:1)

$C_8H_8N_2O_3S$

ESI-mass spectrum: m/z = 211 $[M-H^-]$

The following compounds are prepared analogously to Example E:

5-phenylaminosulphonyl-2-indolinone

Prepared from 5-chlorosulphonyl-2-indolinone and aniline

5-(N-methyl-N-phenyl-aminosulphonyl)-2-indolinone

Prepared from 5-chlorosulphonyl-2-indolinone and N-methyl-aniline

5-(N-butyl-N-methyl-aminosulphonyl)-2-indolinone

Prepared from 5-chlorosulphonyl-2-indolinone and N-methyl-butylamine

5-(3-pyridyl-aminosulphonyl)-2-indolinone
Prepared from 5-chlorosulphonyl-2-indolinone and 3-aminopyridine

5-(3-nitrophenyl-aminosulphonyl)-2-indolinone
Prepared from 5-chlorosulphonyl-2-indolinone and 3-aminonitrotoluene

Example F

1-acetyl-5-methylmercapto-2-indolinone
0.7 g of 5-methylmercapto-2-indolinone are dissolved in 10.4 ml of glacial acetic acid and 3.7 ml of concentrated hydrochloric acid. To this solution are added 5.0 ml of acetic anhydride and the mixture is stirred for 5 hours at 110°C. The solvent is removed, the residue is combined with 100 ml of ice-water and made alkaline with sodium hydroxide solution. The aqueous phase is extracted with methylene chloride and the organic phase is dried over sodium sulphate. After elimination of the solvent the product is recrystallised from petroleum ether.
Yield: 0.6 g of (69 % of theory),
R_f value: 0.12 (silica gel, methylene chloride)
$C_{11}H_{11}NO_2S$
Melting point: 112-114°C

Example G

1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-methylmercapto-2-indolinone
0.6 g of 1-acetyl-5-methylmercapto-2-indolinone and 3.0 ml of triethyl orthobenzoate are stirred for 2 hours in 10 ml of acetic anhydride at 100°C. After this time another 10 ml of acetic anhydride and 3 ml of orthoester are added and the

resulting mixture is heated for 4 hours with stirring. The solvent is removed and the residue is purified through a silica gel column with methylene chloride/cyclohexane (8:2).
Yield: 0.8 g of (78 % of theory),
R_f value: 0.33 (silica gel, methylene chloride/cyclohexane = 8:2)
$C_{20}H_{19}NO_3S$
mass spectrum: m/z = 353 [M^+]

Example H

1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-methoxy-2-indolinone
1.1 g of 5-methoxy-2-indolinone (prepared according to Quallich, G. J.; Morrissey, P. M.; Synthesis 1993, 51), 4.6 ml of triethyl orthobenzoate and 11 ml of acetic anhydride are stirred for 20 hours at 100°C. The solvent is removed and the residue is separated through a silica gel column with petroleum ether/methylene chloride/ethyl acetate (5:4:1).
Yield: 0.7 g of (29 % of theory),
R_f value: 0.6 (silica gel, petroleum ether/methylene chloride/ethyl acetate = 5:4:1)
$C_{20}H_{19}NO_4$
mass spectrum: m/z = 337 [M^+]

The following compounds are prepared analogously to Example H:

(1) 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-diethoxy-phosphoryl-2-indolinone
Prepared from 5-diethoxyphosphoryl-2-indolinone, triethyl orthobenzoate and acetic anhydride

(2) 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-cyano-2-indolinone
Prepared from 5-cyano-2-indolinone (according to Tetrahedron Lett. 28, 4027 (1987)), triethyl orthobenzoate and acetic anhydride

(3) 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-(N-acetyl-aminosulphonyl)-2-indolinone
Prepared from 5-aminosulphonyl-2-indolinone, triethyl orthobenzoate and acetic anhydride

(4) 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-phenylaminosulphonyl-2-indolinone
Prepared from 5-phenylaminosulphonyl-2-indolinone, triethyl orthobenzoate and acetic anhydride

(5) 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-(N-methyl-N-phenyl-aminosulphonyl)-2-indolinone
Prepared from 5-(N-methyl-N-phenyl-aminosulphonyl)-2-indolinone, triethyl orthobenzoate and acetic anhydride

(6) 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-(N-butyl-N-methyl-aminosulphonyl)-2-indolinone
Prepared from 5-(N-butyl-N-methyl-aminosulphonyl)-2-indolinone, triethyl orthobenzoate and acetic anhydride

(7) 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-(3-pyridyl-aminosulphonyl)-2-indolinone
Prepared from 5-(3-pyridyl-aminosulphonyl)-2-indolinone, triethyl orthobenzoate and acetic anhydride

(8) 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-(3-pyridyl-aminosulphonyl)-2-indolinone
Prepared from 5-(3-nitrophenyl-aminosulphonyl)-2-indolinone, triethyl orthobenzoate and acetic anhydride

(9) 1-acetyl-3-(1-ethoxy-1-methyl-methylene)-5-cyano-2-indolinone
Prepared from 5-cyano-2-indolinone (according to Tetrahedron Lett. 28, 4027 (1987), triethyl orthoacetate and acetic anhydride

Example I

N-(2-dimethylamino-ethyl)-N-methylsulphonyl-4-nitroaniline

38.9 g of N-methylsulphonyl-4-nitroaniline are dissolved in 2.0 l of acetone, 51.9 g of 1-chloro-2-dimethylamino-ethane, 77.4 g of potassium carbonate and 5.0 g of sodium iodide are added and the mixture is stirred for a total of 4 days at 50°C; after 12 hours another 25.9 g of 1-chloro-2-dimethylamino-ethane, 49.8 g of potassium carbonate and 5.0 g of sodium iodide in 500 ml of acetone are added and after 36 hours another 26.0 g of 1-chloro-2-dimethylamino-ethane, 50.0 g of potassium carbonate and 5.0 g of sodium iodide in 100 ml of acetone are added. After this time the mixture is filtered and the filtrate is evaporated down. The residue is mixed with ether, suction filtered and dried at 40°C.

Yield: 25.3 g of (49 % of theory),

R_f value: 0.5 (silica gel, methylene chloride/methanol/ammonia = 9:1:0.1)

$C_{11}H_{17}N_3O_4S$

ESI-mass spectrum: m/z = 288 $[M+H^+]$

The following compound is prepared analogously to Example I:

(1) N-carboxymethyl-N-methylsulphonyl-4-nitroaniline

Example J

N-(dimethylcarbamoyl-methyl)-N-methylsulphonyl-4-nitroaniline

7.0 g of N-carboxymethyl-N-methylsulphonyl-4-nitroaniline, 2.5 g of dimethylamine hydrochloride, 8.1 g of TBTU and 3.9 g of HOBT are dissolved in 125 ml of dimethylformamide and at 0°C 17.6 ml of N-ethyl-diisopropylamine are added. The mixture is stirred for 4 hours at room temperature, diluted with 1 l water and the precipitate formed is suction filtered. After washing with water, ethanol and ether the residue is dried at 70°C *in vacuo*.

Yield: 5.3 g of (69 % of theory),

R_f value: 0.40 (silica gel, methylene chloride/methanol = 9:1)
$C_{11}H_{15}N_3O_5S$
ESI mass spectrum: m/z = 300 $[M-H^-]$

Example K

N-(dimethylaminomethylcarbonyl)-N-methyl-4-nitro-aniline

1.8 g of dimethylamine hydrochloride and 5.5 g of potassium carbonate are placed in 80 ml of acetone and 4.2 g of N-(2-bromomethylcarbonyl)-N-methyl-4-nitroaniline (prepared according to Chem. Ber. 119, 2430 (1986)) are added in three batches at room temperature. The mixture is stirred for 12 hours at room temperature. After this time the mixture is filtered and the filtrate is evaporated down. The residue is dissolved in ethyl acetate, washed twice with water, dried over sodium sulphate and finally concentrated by rotary evaporation.
Yield: 2.8 g of (79 % of theory),
R_f value: 0.5 (silica gel, ethyl acetate/methanol = 7:3)
Melting point: 121-122°C

Example L

4-(piperidin-1-yl-methyl)-nitrobenzene

40.0 g of 4-nitrobenzylbromide are dissolved in 500 ml of methylene chloride, 51.5 ml of triethylamine are added and 18.3 ml of piperidine are carefully added dropwise. After the exothermic reaction has ended the mixture is refluxed for another 30 minutes. After cooling it is washed with water and the organic phase is dried over sodium sulphate. Finally, the organic phase is evaporated down.
Yield: 36.3 g of (89 % of theory),
R_f value: 0.6 (silica gel, methylene chloride/methanol = 9:1)
$C_{12}H_{16}N_2O_2$
mass spectrum: m/z = 221 $[M^+]$

The following compounds are prepared analogously to Example L:

(1) 4-[(N-benzyl-N-methyl-amino)-methyl]-nitrobenzene

(2) 3-(dimethylaminomethyl)-nitrobenzene

(3) 4-(dimethylaminomethyl)-nitrobenzene

(4) 4-(2-dimethylamino-ethyl)-nitrobenzene

(5) 4-(2,3,4,5-tetrahydro-benzo(d)azepin-3-yl)-methyl]-nitrobenzene

Example M

4-(4-methyl-piperazin-1-yl)-nitrobenzene

31.5 g of 4-chloro-1-nitrobenzene and 44.4 ml of 1-methylpiperazine are combined and stirred for 18 hours at 90°C. Then the solution is poured onto ice-water and the precipitate formed is suction filtered, washed with water and recrystallised from ethanol/water 1:1. The residue is dried *in vacuo* at 75°C.

Yield: 44.0 g of (99 % of theory),
R_f value: 0.5 (silica gel, methylene chloride/methanol = 10:1)
Melting point: 108-112°C

The following compound is prepared analogously to Example M:

(1) 4-(Morpholin-4-yl)-nitrobenzene

Example N

4-(piperidin-1-yl-methyl)-aniline

37.0 g of 4-(piperidin-1-yl-methyl)-nitrobenzene are dissolved in 300 ml of methanol, 8.0 g of Raney nickel are added and the mixture is hydrogenated for 1 hour 25 minutes with 3 bars of

hydrogen at room temperature. The catalyst is filtered off and the filtrate is concentrated by evaporation.
Yield: 24.0 g (75 % of theory),
R_f value: 0.4 (silica gel, methylene chloride/methanol = 9:1)
$C_{12}H_{18}N_2$
ESI mass spectrum: m/z = 191 $[M+H^+]$

The following compounds are prepared analogously to Example M:

(1) 4-[(N-benzyl-N-methyl-amino)-methyl]-aniline

(2) N-(2-dimethylamino-ethyl)-N-methylsulphonyl-p-phenylene-diamine

(3) 3-(dimethylaminomethyl)-aniline

(4) 4-(dimethylaminomethyl)-aniline

(5) N-(dimethylaminomethylcarbonyl)-N-methyl-p-phenylene-diamine

(6) N-(dimethylcarbamoyl-methyl)-N-methylsulphonyl-p-phenylene-diamine

(7) 4-(2-dimethylamino-ethyl)-aniline

(8) 4-(2,3,4,5-tetrahydro-benzo(d)azepin-3-yl)-methyl]-aniline

(9) 4-(4-methyl-piperazin-1-yl)-aniline

(10) 4-(Morpholin-4-yl)-aniline

Example O

3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-5-(N-acetyl-aminosulphonyl)-2-indolinone

780 mg of 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-(N-acetyl-aminosulphonyl)-2-indolinone are dissolved in 6.0 ml of dimethylformamide and 300 mg of 4-(dimethylaminomethyl)-aniline are added. The mixture is stirred for 4 hours at 110°C. After cooling the solvent is eliminated and the residue is dissolved in 20 ml of methanol and 20 ml of dichloromethane. 5.0 ml of concentrated ammonia are added to this mixture and it is stirred for 1 hour at room temperature. After elimination of the solvent the residue is purified through a silica gel column with methylene chloride/methanol (4:1).

Yield: 150 mg (18 % of theory),

R_f value: 0.29 (silica gel, methylene chloride/methanol = 9:1)

$C_{26}H_{26}N_4O_4S$

mass spectrum: m/z = 490 [M^+]

Preparation of the final compounds:

Example 1

3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-methoxy-2-indolinone

0.3 g of 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-methylmercap-to-2-indolinone and 0.3 g of 4-(piperidin-1-yl-methyl)-aniline are dissolved in 3.0 ml of dimethylformamide and stirred for 2 hours at 110°C. After cooling 1.0 ml of piperidine is added and the mixture is stirred for 3 hours at room temperature, combined with water and the precipitate formed is suction filtered. The precipitate is washed with water, isopropanol and ether and dried *in vacuo* at 100°C.

Yield: 200 mg (44 % of theory),

R_f value: 0.5 (silica gel, methylene chloride/methanol = 5:1)

$C_{28}H_{29}N_3O_2$

mass spectrum: m/z = 439 [M^+]

The following compounds are prepared analogously to Example 1:

(1) 3-Z-[1-(4-methoxy-anilino)-1-phenyl-methylene]-5-methoxy-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-methoxy-2-indolinone and p-anisidine

R_f value: 0.2 (silica gel, toluene/ethyl acetate = 5:1)

$C_{23}H_{20}N_2O_3$

mass spectrum: m/z = 372 [M^+]

(2) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-methylmercapto-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-methylmercapto-2-indolinone and 4-(piperidin-1-yl-methyl)-aniline

R_f value: 0.27 (silica gel, methylene chloride/ethanol = 9:1)

$C_{28}H_{29}N_3OS$

ESI mass spectrum: m/z = 456 [$M+H^+$]

(3) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene)-5-diethoxyphosphoryl-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-diethoxyphosphoryl-2-indolinone and 4-(piperidin-1-yl-methyl)-aniline
R_f value: 0.7 (aluminium oxide, ethyl acetate/ethanol = 10:1)
$C_{31}H_{36}N_3O_4P$
mass spectrum: m/z = 545 [M^+]

(4) 3-Z-[1-(4-((N-benzyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-diethoxyphosphoryl-2-indolinone and 4-[(N-benzyl-N-methyl-amino)-methyl]-aniline
R_f value: 0.5 (silica gel, methylene chloride/ethanol = 10:1)
$C_{34}H_{36}N_3O_4P$
mass spectrum: m/z = 581 [M^+]

(5) 3-Z-[1-(3-(dimethylaminomethyl)-anilino)-1-phenyl-methylene)-5-diethoxyphosphoryl-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-diethoxyphosphoryl-2-indolinone and 3-(dimethylaminomethyl)-aniline
R_f value: 0.6 (silica gel, methylene chloride/ethanol/ammonia = 5:1:0.01)
$C_{28}H_{32}N_3O_4P$
mass spectrum: m/z = 505 [M^+]

(6) 3-Z-[1-(4-chloro-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-diethoxyphosphoryl-2-indolinone and 4-chloroaniline
R_f value: 0.6 (silica gel, methylene chloride/ethanol= 10:1)
$C_{25}H_{24}ClN_2O_4P$
ESI mass spectrum: m/z = 505/507 [$M+Na^+$]

(7) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-diethoxyphosphoryl-2-indolinone and N-(2-dimethylamino-ethyl)-N-methylsulphonyl-p-phenylene-diamine
R_f value: 0.4 (silica gel, methylene chloride/ethanol = 5:1)
$C_{30}H_{37}N_4O_6PS$
mass spectrum: m/z = 612 [M^+]

(8) 3-Z-[1-(4-(N-(dimethylaminocarbonyl-methyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-diethoxyphosphoryl-2-indolinone and N-(dimethylcarbamoyl-methyl)-N-methylsulphonyl-p-phenylene-diamine
R_f value: 0.6 (silica gel, ethyl acetate/ethanol = 5:1)
$C_{30}H_{35}N_4O_7PS$
mass spectrum: m/z = 626 [M^+]

(9) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-diethoxyphosphoryl-2-indolinone and N-(dimethylaminomethyl-carbonyl)-N-methyl-p-phenylene-diamine
R_f value: 0.6 (aluminium oxide, methylene chloride/ethanol = 10:1)
$C_{30}H_{35}N_4O_5P$
mass spectrum: m/z = 562 [M^+]

(10) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene)-5-cyano-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-cyano-2-indolinone and 4-(piperidin-1-yl-methyl)-aniline
R_f value: 0.3 (silica gel, methylene chloride/methanol 9:1)
$C_{28}H_{26}N_4O$
mass spectrum: m/z = 434 [M^+]

(11) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-phenylaminosulphonyl-2-indolinone and 4-(piperidin-1-yl-methyl)-aniline
R_f value: 0.17 (silica gel, methylene chloride/methanol = 9:1)
$C_{33}H_{32}N_4O_3S$
ESI mass spectrum: m/z = 563 $[M-H^-]$

(12) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-(N-methyl-N-phenyl-aminosulphonyl)-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-(N-methyl-N-phenyl-aminosulphonyl)-2-indolinone and 4-(piperidin-1-yl-methyl)-aniline
R_f value: 0.22 (silica gel, methylene chloride/methanol = 9:1)
$C_{34}H_{34}N_4O_3S$
ESI mass spectrum: m/z = 577 $[M-H^-]$

(13) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-(N-butyl-N-methyl-aminosulphonyl)-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-(N-butyl-N-methyl-aminosulphonyl)-2-indolinone and 4-(piperidin-1-yl-methyl)-aniline
R_f value: 0.19 (silica gel, methylene chloride/methanol = 9:1)
$C_{32}H_{38}N_4O_3S$
ESI mass spectrum: m/z = 557 $[M-H^-]$

(14) 3-Z-[1-(4-(2-dimethylamino-ethyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-phenylaminosulphonyl-2-indolinone and 4-(2-dimethylamino-ethyl)-aniline
R_f value: 0.17 (silica gel, methylene chloride/methanol = 9:1)
$C_{31}H_{30}N_4O_3S$
ESI mass spectrum: m/z = 537 $[M-H^-]$

(15) 3-Z-[1-(4-(dimethylamino-methyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-phenylaminosulphonyl-2-indolinone and 4-(dimethylamino-methyl)-aniline
R_f value: 0.18 (silica gel, methylene chloride/methanol = 9:1)
$C_{30}H_{28}N_4O_3S$
ESI mass spectrum: m/z = 523 [M-H$^-$]

(16) 3-Z-[1-((1-methyl-piperidin-4-yl)-amino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-phenylaminosulphonyl-2-indolinone and 4-amino-methyl-piperidine
R_f value: 0.20 (silica gel, methylene chloride/methanol = 9:1)
$C_{27}H_{28}N_4O_3S$
ESI mass spectrum: m/z = 487 [M-H$^-$]

(17) 3-Z-(1-anilino-1-phenyl-methylene)-5-(phenyl-aminosulphonyl)-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-phenylaminosulphonyl-2-indolinone and aniline
R_f value: 0.66 (silica gel, methylene chloride/methanol = 9:1)
$C_{27}H_{21}N_3O_3S$
mass spectrum: m/z = 467 [M$^+$]

(18) 3-Z-[1-(4-acetylamino-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-phenylaminosulphonyl-2-indolinone and 4-aminoacetanilide
R_f value: 0.60 (silica gel, methylene chloride/methanol = 9:1)
$C_{29}H_{24}N_4O_4S$
mass spectrum: m/z = 524 [M$^+$]

(19) 3-Z-[1-(3-dimethylaminomethyl-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-phenylaminosulphonyl-2-indolinone and 3-(dimethylamino-methyl)-aniline
R_f value: 0.32 (silica gel, methylene chloride/methanol = 9:1)
$C_{30}H_{28}N_4O_3S$
mass spectrum: m/z = 524 [M^+]

(20) 3-Z-[1-(4-(N-benzyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-phenylaminosulphonyl-2-indolinone and 4-[(N-benzyl-N-methyl-amino)-methyl]-aniline
R_f value: 0.63 (silica gel, methylene chloride/methanol = 9:1)
$C_{36}H_{32}N_4O_3S$
ESI mass spectrum: m/z = 601 [$M+H^+$]

(21) 3-Z-(1-(4-(2,3,4,5-tetrahydro-benzo(d)azepin-3-yl)-methyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-phenylaminosulphonyl-2-indolinone and 4-(2,3,4,5-tetrahydro-benzo(d)azepin-3-yl)-methyl]-aniline
R_f value: 0.63 (silica gel, methylene chloride/methanol = 9:1)
$C_{38}H_4N_4O_3S$
ESI mass spectrum: m/z = 626 [M^+]

(22) 3-Z-[1-(4-(N-methyl-acetylamino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-phenylaminosulphonyl-2-indolinone and 4-amino-N-methyl-acetanilide
R_f value: 0.52 (silica gel, methylene chloride/methanol = 9:1)
$C_{30}H_{26}N_4O_4S$
mass spectrum: m/z = 538 [M^+]

(23) 3-Z-[1-(4-(N-methyl-piperazin-1-yl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-phenylaminosulphonyl-2-indolinone and 4-(N-methyl-piperazin-1-yl)-aniline
R_f value: 0.18 (silica gel, methylene chloride/methanol = 9:1)
$C_{32}H_{31}N_5O_3S$
mass spectrum: m/z = 565 [M^+]

(24) 3-Z-[1-(4-(morpholin-4-yl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-phenylaminosulphonyl-2-indolinone and 4-morpholin-4-yl-aniline
R_f value: 0.61 (silica gel, methylene chloride/methanol = 9:1)
$C_{31}H_{28}N_4O_4S$
ESI mass spectrum: m/z = 551 [$M-H^-$]

(25) 3-Z-[1-(4-toluenesulphonylamino-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-phenylaminosulphonyl-2-indolinone and N-(4-aminophenyl)-toluenesulphonic acid amide
R_f value: 0.53 (silica gel, methylene chloride/methanol = 9:1)
$C_{34}H_{28}N_4O_5S_2$
mass spectrum: m/z = 636 [M^+]

(26) 3-Z-[1-(4-(dimethylamino-methyl)-anilino)-1-phenyl-methylene]-5-(3-pyridyl-aminosulphonyl)-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-(3-pyridylaminosulphonyl)-2-indolinone and 4-(dimethylamino-methyl)-aniline
R_f value: 0.28 (silica gel, methylene chloride/methanol = 9:1)
$C_{29}H_{27}N_5O_3S$
ESI mass spectrum: m/z = 524 [$M-H^-$]

(27) 3-Z-[1-(4-(dimethylamino-methyl)-anilino)-1-phenyl-methylene]-5-(3-nitrophenyl-aminosulphonyl)-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-(3-nitrophenyl-aminosulphonyl)-2-indolinone and 4-(dimethylamino-methyl)-aniline
R_f value: 0.25 (silica gel, methylene chloride/methanol = 9:1)
$C_{30}H_{27}N_5O_5S$
ESI mass spectrum: m/z = 568 $[M-H^-]$

(28) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-methyl-methylene)-5-cyano-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-methyl-methylene)-5-cyano-2-indolinone and 4-(piperidin-1-yl-methyl)-aniline
R_f value: 0.77 (silica gel, methylene chloride/methanol 8:2)
$C_{23}H_{24}N_4O$
mass spectrum: m/z = 373 $[M+H^-]$

(29) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-(3-pyridyl-aminosulphonyl)-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-(3-pyridylaminosulphonyl)-2-indolinone and 4-(piperidin-1-yl-methyl)-aniline
R_f value: 0.12 (silica gel, methylene chloride/methanol = 9:1)
$C_{32}H_{31}N_5O_3S$
ESI mass spectrum: m/z = 564 $[M-H^-]$

(30) 3-Z-[1-(4-(2,3,4,5-tetrahydro-benz[d]azepin-3-yl-methyl)-anilino)-1-phenyl-methylene]-5-cyano-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-cyano-2-indolinone and 4-(2,3,4,5-tetrahydro-benz[d]azepin-3-yl-methyl)-aniline
R_f value: 0.4 (silica gel, methylene chloride/methanol/ammonia 9:1:0.1)
$C_{33}H_{28}N_4O$
mass spectrum: m/z = 495 $[M-H^-]$

(31) 3-Z-[1-(4-(dimethylamino-methyl)-anilino)-1-phenyl-methylene]-5-cyano-2-indolinone
Prepared from 1-acetyl-3-(1-ethoxy-1-phenyl-methylene)-5-cyano-2-indolinone and 4-(dimethylamino-methyl)-aniline
R_f value: 0.3 (silica gel, methylene chloride/methanol/ammonia 9:1:0.1)
$C_{25}H_{22}N_4O$
mass spectrum: m/z = 395 $[M+H^+]$

Example 2

3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-5-aminosulphonyl-2-indolinone

100 mg of 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-5-(N-acetyl-aminosulphonyl)-2-indolinone are dissolved in 10 ml of ethanol and 5.0 ml of 1N hydrochloric acid are added. The mixture is stirred for two weeks at room temperature. After this time 5.0 ml of 1N sodium hydroxide solution are added and the solution is evaporated down. The residue is taken up in a little methylene chloride and methanol and filtered. The filtrate is evaporated down and purified through a silica gel column with ethyl acetate/cyclohexane/methanol (2:2:6).
Yield: 39 mg (33 % of theory),
R_f value: 0.19 (silica gel, ethyl acetate/cyclohexane/methanol = 2:2:6)
$C_{24}H_{24}N_4O_3S$
mass spectrum: m/z = 448 $[M^+]$

Example 3

3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-methylsulphinyl-2-indolinone

200 mg 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-methylmercapto-2-indolinone are dissolved in 2.0 ml of glacial acetic acid and 330 mg of hydrogen peroxide (35% strength) in 20 ml of glacial acetic acid are added. The mixture is stirred for 5 hours at room temperature. After this

time the solvent is eliminated, the mixture is neutralised with dilute ammonia solution and dried over sodium sulphate. The residue is purified through a silica gel column with methylene chloride/ethanol (9:1).
Yield: 0.2 g (87 % of theory),
R_f value: 0.25 (silica gel, methylene chloride/ethanol = 9:1)
$C_{28}H_{29}N_3O_2S$
ESI mass spectrum: m/z = 472 $[M+H^+]$

The following compound is prepared analogously to Example 3:

(1) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-methylsulphonyl-2-indolinone
Prepared from 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-methylsulphinyl-2-indolinone and hydrogen peroxide (35%)
R_f value: 0.19 (silica gel, methylene chloride/ethanol = 9:1)
$C_{28}H_{29}N_3O_3S$
mass spectrum: m/z = 487 $[M^+]$

The following compounds may be prepared analogously to the foregoing Examples:

(1) 3-Z-(1-anilino-1-phenyl-methylene)-5-diethoxyphosphoryl-2-indolinone

(2) 3-Z-[1-(4-nitro-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(3) 3-Z-[1-(4-ethoxycarbonyl-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(4) 3-Z-[1-(4-carboxy-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(5) 3-Z-[1-(4-fluoro-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(6) 3-Z-[1-(4-bromo-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(7) 3-Z-[1-(4-iodo-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(8) 3-Z-[1-(4-cyano-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(9) 3-Z-[1-(4-methoxy-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(10) 3-Z-[1-(4-ethoxy-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(11) 3-Z-[1-(4-trifluoromethyl-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(12) 3-Z-[1-(4-methyl-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(13) 3-Z-[1-(4-methylmercapto-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(14) 3-Z-[1-(4-aminomethyl-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(15) 3-Z-[1-(4-methylaminomethyl-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(16) 3-Z-[1-(4-isopropylaminomethyl-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(17) 3-Z-[1-(4-phenylaminomethyl-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(18) 3-Z-[1-(4-ethylaminomethyl-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(19) 3-Z-[1-(4-propylaminomethyl-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(20) 3-Z-[1-(4-butylaminomethyl-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(21) 3-Z-[1-(4-isobutylaminomethyl-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(22) 3-Z-[1-(4-cyclohexylaminomethyl-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(23) 3-Z-[1-(4-benzylaminomethyl-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(24) 3-Z-[1-(4-dimethylaminomethyl-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(25) 3-Z-[1-(4-((N-ethyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(26) 3-Z-[1-(4-diethylaminomethyl-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(27) 3-Z-[1-(4-((N-methyl-N-propyl-amino)-methyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(28) 3-Z-[1-(4-((N-isopropyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(29) 3-Z-[1-(4-((N-ethyl-N-propyl-amino)-methyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(30) 3-Z-[1-(4-((N-ethyl-N-isopropyl-amino)-methyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(31) 3-Z-[1-(4-dipropylaminomethyl-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(32) 3-Z-[1-(4-diisopropylaminomethyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(33) 3-Z-[1-(4-((N-benzyl-N-ethyl-amino)-methyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(34) 3-Z-[1-(4-dibenzylaminomethyl-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(35) 3-Z-[1-(4-(pyrrolidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(36) 3-Z-[1-(4-(3,6-dihydro-2H-pyridin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(37) 3-Z-[1-(4-(2,6-dimethyl-piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(38) 3-Z-[1-(4-(3,5-dimethyl-piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(39) 3-Z-[1-(4-(azepan-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(40) 3-Z-[1-(4-(piperazin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(41) 3-Z-[1-(4-(morpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(42) 3-Z-[1-(4-(thiomorpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(43) 3-Z-[1-(4-(1-oxo-thiomorpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(44) 3-Z-[1-(4-(acetylamino-methyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(45) 3-Z-[1-(4-(2-aminoethyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(46) 3-Z-[1-(4-(2-methylamino-ethyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(47) 3-Z-[1-(4-(2-ethylamino-ethyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(48) 3-Z-[1-(4-(2-dimethylamino-ethyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(49) 3-Z-[1-(4-(2-diethylamino-ethyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(50) 3-Z-[1-(4-(2-piperidin-1-yl-ethyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(51) 3-Z-[1-(4-(2-(4-ethoxycarbonyl-piperidin-1-yl)-ethyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(52) 3-Z-[1-(4-(2-(4-carboxy-piperidin-1-yl)-ethyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(53) 3-Z-[1-(4-(2-(4-dimethylcarbamoyl-piperidin-1-yl)-ethyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(54) 3-Z-[1-(4-(2-acetylamino-ethyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(55) 3-Z-[1-(4-(3-amino-propyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(56) 3-Z-[1-(4-(3-dimethylamino-propyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(57) 3-Z-[1-(4-(N-aminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(58) 3-Z-[1-(4-(N-methylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(59) 3-Z-[1-(4-(N-ethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(60) 3-Z-[1-(4-(N-diethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(61) 3-Z-[1-(4-(N-(piperidin-1-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(62) 3-Z-[1-(4-(N-(morpholin-4-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(63) 3-Z-[1-(4-(N-(piperazin-1-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(64) 3-Z-[1-(4-(N-(2-amino-ethylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(65) 3-Z-[1-(4-(N-(2-methylamino-ethylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(66) 3-Z-[1-(4-(N-(2-diethylamino-ethylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(67) 3-Z-[1-(4-(N-acetyl-N-(2-aminoethyl)-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(68) 3-Z-[1-(4-(N-acetyl-N-(2-methylamino-ethyl)-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(69) 3-Z-[1-(4-(N-acetyl-N-(2-dimethylaminoethyl)-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(70) 3-Z-[1-(4-(N-acetyl-N-(3-amino-propyl)-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(71) 3-Z-[1-(4-(N-acetyl-N-(3-dimethylamino-propyl)-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(72) 3-Z-[1-(4-(N-acetyl-N-(3-methylamino-propyl)-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(73) 3-Z-[1-(4-(N-acetyl-N-(2-piperidin-1-yl-ethyl)-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(74) 3-Z-[1-(4-(N-acetyl-N-carbamoylmethyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(75) 3-Z-[1-(4-(N-acetyl-N-dimethylcarbamoylmethyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(76) 3-Z-[1-(4-(N-acetyl-N-(piperidin-1-yl-carbonylmethyl)-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(77) 3-Z-[1-(4-(N-methyl-N-carbamoyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(78) 3-Z-[1-(4-(N-methyl-N-methylcarbamoyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(79) 3-Z-[1-(4-(N-methyl-N-dimethylcarbamoyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(80) 3-Z-[1-(4-(N-methyl-N-(piperidin-1-yl-carbonyl)-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(81) 3-Z-[1-(4-(N-(2-aminoethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(82) 3-Z-[1-(4-(N-(2-methylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(83) 3-Z-[1-(4-(N-(2-ethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(84) 3-Z-[1-(4-(N-(2-diethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(85) 3-Z-[1-(4-(N-(2-pyrrolidin-1-yl-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(86) 3-Z-[1-(4-(N-(2-piperidin-1-yl-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(87) 3-Z-[1-(4-(N-(2-piperazin-1-yl-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(88) 3-Z-[1-(4-(N-(2-morpholin-4-yl-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(89) 3-Z-[1-(4-(N-carbamoylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(90) 3-Z-[1-(4-(N-methylcarbamoylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(91) 3-Z-[1-(4-(N-ethylcarbamoylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(92) 3-Z-[1-(4-(N-((2-dimethylamino-ethyl)-carbamoylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(93) 3-Z-[1-(4-(N-(N-(2-dimethylamino-ethyl)-N-methyl-carbamoylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(94) 3-Z-[1-(4-(N-diethylcarbamoylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(95) 3-Z-[1-(4-(N-(pyrrolidin-1-yl-carbonylmethyl)-N-methyl-sulphonyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(96) 3-Z-[1-(4-(N-(piperidin-1-yl-carbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(97) 3-Z-[1-(4-(N-(piperazin-1-yl-carbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(98) 3-Z-[1-(4-(N-(morpholin-4-yl-carbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(99) 3-Z-[1-(4-(2-dimethylamino-ethoxy)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(100) 3-Z-[1-(4-(3-dimethylamino-propoxy)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(101) 3-Z-[1-(4-carbamoylmethyl-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(102) 3-Z-[1-(4-(2-carbamoyl-ethyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(103) 3-Z-[1-(4-(1H-imidazol-4-yl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(104) 3-Z-[1-(4-(pyridin-2-yl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(105) 3-Z-[1-(4-(pyridin-3-yl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(106) 3-Z-[1-(4-(pyridin-4-yl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(107) 3-Z-(1-anilino-1-phenyl-methylene)-5-(phenyl-aminosulphonyl)-2-indolinone

(108) 3-Z-[1-(4-nitro-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(109) 3-Z-[1-(4-ethoxycarbonyl-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(110) 3-Z-[1-(4-carboxy-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(111) 3-Z-[1-(4-fluoro-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(112) 3-Z-[1-(4-chloro-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(113) 3-Z-[1-(4-bromo-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(114) 3-Z-[1-(4-iodo-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(115) 3-Z-[1-(4-cyano-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(116) 3-Z-[1-(4-methoxy-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(117) 3-Z-[1-(4-ethoxy-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(118) 3-Z-[1-(4-trifluoromethyl-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(119) 3-Z-[1-(4-methyl-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(120) 3-Z-[1-(4-methylmercapto-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(121) 3-Z-[1-(4-aminomethyl-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(122) 3-Z-[1-(4-methylaminomethyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(123) 3-Z-[1-(4-isopropylaminomethyl-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(124) 3-Z-[1-(4-phenylaminomethyl-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(125) 3-Z-[1-(4-ethylaminomethyl-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(126) 3-Z-[1-(4-propylaminomethyl-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(127) 3-Z-[1-(4-butylaminomethyl-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(128) 3-Z-[1-(4-isobutylaminomethyl-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(129) 3-Z-[1-(4-cyclohexylaminomethyl-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(130) 3-Z-[1-(4-benzylaminomethyl-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(132) 3-Z-[1-(3-dimethylaminomethyl-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(133) 3-Z-[1-(4-((N-ethyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(134) 3-Z-[1-(4-diethylaminomethyl-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(135) 3-Z-[1-(4-((N-methyl-N-propyl-amino)-methyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(136) 3-Z-[1-(4-((N-isopropyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(137) 3-Z-[1-(4-((N-ethyl-N-propyl-amino)-methyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(138) 3-Z-[1-(4-((N-ethyl-N-isopropyl-amino)-methyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(139) 3-Z-[1-(4-dipropylaminomethyl-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(140) 3-Z-[1-(4-diisopropylaminomethyl-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(141) 3-Z-[1-(4-((N-benzyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(142) 3-Z-[1-(4-((N-benzyl-N-ethyl-amino)-methyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(143) 3-Z-[1-(4-dibenzylaminomethyl-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(144) 3-Z-[1-(4-(pyrrolidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(145) 3-Z-[1-(4-(3,6-dihydro-2H-pyridin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(146) 3-Z-[1-(4-(2,6-dimethyl-piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(147) 3-Z-[1-(4-(3,5-dimethyl-piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(148) 3-Z-[1-(4-(azepan-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(149) 3-Z-[1-(4-(piperazin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(150) 3-Z-[1-(4-(morpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(151) 3-Z-[1-(4-(thiomorpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(152) 3-Z-[1-(4-(1-oxo-thiomorpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(153) 3-Z-[1-(4-acetylaminomethyl-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(154) 3-Z-[1-(4-(2-amino-ethyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(155) 3-Z-[1-(4-(2-methylamino-ethyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(156) 3-Z-[1-(4-(2-ethylamino-ethyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(157) 3-Z-[1-(4-(2-diethylamino-ethyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(158) 3-Z-[1-(4-(2-piperidin-1-yl-ethyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(159) 3-Z-[1-(4-(2-(4-ethoxycarbonyl-piperidin-1-yl)-ethyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(160) 3-Z-[1-(4-(2-(4-carboxy-piperidin-1-yl)-ethyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(161) 3-Z-[1-(4-(2-(4-dimethylcarbamoyl-piperidin-1-yl)-ethyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(162) 3-Z-[1-(4-(2-acetylamino-ethyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(163) 3-Z-[1-(4-(3-aminopropyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(164) 3-Z-[1-(4-(3-dimethylamino-propyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(165) 3-Z-[1-(4-(N-aminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(166) 3-Z-[1-(4-(N-methylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(167) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(168) 3-Z-[1-(4-(N-ethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(169) 3-Z-[1-(4-(N-diethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(170) 3-Z-[1-(4-(N-(piperidin-1-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(171) 3-Z-[1-(4-(N-(morpholin-4-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(172) 3-Z-[1-(4-(N-(piperazin-1-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(173) 3-Z-[1-(4-(N-(2-amino-ethylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(174) 3-Z-[1-(4-(N-(2-methylamino-ethylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(175) 3-Z-[1-(4-(N-(2-diethylamino-ethylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(176) 3-Z-[1-(4-(N-acetyl-N-(2-aminoethyl)-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(177) 3-Z-[1-(4-(N-acetyl-N-(2-methylamino-ethyl)-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(178) 3-Z-[1-(4-(N-acetyl-N-(2-dimethylaminoethyl)-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(179) 3-Z-[1-(4-(N-acetyl-N-(3-amino-propyl)-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(180) 3-Z-[1-(4-(N-acetyl-N-(3-dimethylamino-propyl)-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(181) 3-Z-[1-(4-(N-acetyl-N-(3-methylamino-propyl)-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(182) 3-Z-[1-(4-(N-acetyl-N-(2-piperidin-1-yl-ethyl)-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(183) 3-Z-[1-(4-(N-acetyl-N-(carbamoylmethyl)-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(184) 3-Z-[1-(4-(N-acetyl-N-dimethylcarbamoylmethyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(185) 3-Z-[1-(4-(N-ethylcarbonyl-N-dimethylcarbamoylmethyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(186) 3-Z-[1-(4-(N-acetyl-N-(piperidin-1-yl-carbonylmethyl)-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(187) 3-Z-[1-(4-(N-methyl-N-carbamoyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(188) 3-Z-[1-(4-(N-methyl-N-methylcarbamoyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(189) 3-Z-[1-(4-(N-methyl-N-dimethylcarbamoyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(190) 3-Z-[1-(4-(N-methyl-N-(piperidin-1-yl-carbonyl)-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(191) 3-Z-[1-(4-(N-(2-aminoethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(192) 3-Z-[1-(4-(N-(2-methylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(193) 3-Z-[1-(4-(N-(2-ethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(194) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(195) 3-Z-[1-(4-(N-(2-diethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(196) 3-Z-[1-(4-(N-(2-pyrrolidin-1-yl-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(197) 3-Z-[1-(4-(N-(2-piperidin-1-yl-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(198) 3-Z-[1-(4-(N-(2-piperazin-1-yl-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(199) 3-Z-[1-(4-(N-(2-morpholin-4-yl-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(200) 3-Z-[1-(4-(N-carbamoylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(201) 3-Z-[1-(4-(N-methylcarbamoylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(202) 3-Z-[1-(4-(N-ethylcarbamoylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(203) 3-Z-[1-(4-(N-((2-dimethylamino-ethyl)-carbamoylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(204) 3-Z-[1-(4-(N-(N-(2-dimethylamino-ethyl)-N-methyl)-carbamoylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(205) 3-Z-[1-(4-(N-dimethylcarbamoylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(206) 3-Z-[1-(4-(N-diethylcarbamoylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(207) 3-Z-[1-(4-(N-(pyrrolidin-1-yl-carbonylmethyl)-N-methyl-sulphonyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-amino-sulphonyl)-2-indolinone

(208) 3-Z-[1-(4-(N-(piperidin-1-yl-carbonylmethyl)-N-methyl-sulphonyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-amino-sulphonyl)-2-indolinone

(209) 3-Z-[1-(4-(N-(piperazin-1-yl-carbonylmethyl)-N-methyl-sulphonyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-amino-sulphonyl)-2-indolinone

(210) 3-Z-[1-(4-(N-(morpholin-4-yl-carbonylmethyl)-N-methyl-sulphonyl-amino)-anilino)-1-phenyl-methylene]-5-(phenyl-amino-sulphonyl)-2-indolinone

(211) 3-Z-[1-(4-(2-dimethylamino-ethoxy)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(212) 3-Z-[1-(4-(3-dimethylamino-propoxy)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(213) 3-Z-[1-(4-carbamoylmethyl-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(214) 3-Z-[1-(4-(2-carbamoyl-ethyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(215) 3-Z-[1-(4-(1H-imidazol-4-yl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(216) 3-Z-[1-(4-(pyridin-2-yl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(217) 3-Z-[1-(4-(pyridin-3-yl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(218) 3-Z-[1-(4-(pyridin-4-yl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(219) 3-Z-[1-(4-(tetrazol-5-yl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(220) 3-Z-[1-(4-(tetrazol-5-yl-methyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(221) 3-Z-[1-(4-(2-(tetrazol-5-yl)-ethyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(222) 3-Z-[1-(4-(3-(tetrazol-5-yl)-propyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone

(223) 3-Z-[1-(4-(tetrazol-5-yl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(224) 3-Z-[1-(4-(tetrazol-5-yl-methyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(225) 3-Z-[1-(4-(2-(tetrazol-5-yl)-ethyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(226) 3-Z-[1-(4-(3-(tetrazol-5-yl)-propyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(227) 3-Z-[1-(4-(pyrrolidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-cyano-2-indolinone

(228) 3-Z-[1-(4-(ethylamino-methyl)-anilino)-1-phenyl-methylene]-5-cyano-2-indolinone

(229) 3-Z-[1-(4-(butylamino-methyl)-anilino)-1-phenyl-methylene]-5-cyano-2-indolinone

(230) 3-Z-[1-(4-(azepin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-cyano-2-indolinone

(231) 3-Z-[1-(4-(ethanolamino-methyl)-anilino)-1-phenyl-methylene]-5-cyano-2-indolinone

(232) 3-Z-[1-(4-(diethanolamino-methyl)-anilino)-1-phenyl-methylene]-5-cyano-2-indolinone

(233) 3-Z-[1-(4-(morpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-5-cyano-2-indolinone

(234) 3-Z-[1-(4-(thiomorpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-5-cyano-2-indolinone

(235) 3-Z-[1-(4-(1-oxo-thiomorpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-5-cyano-2-indolinone

(236) 3-Z-[1-(4-(1,1-dioxo-thiomorpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-5-cyano-2-indolinone

(237) 3-Z-[1-(4-(1-oxo-thiomorpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-5-cyano-2-indolinone

(238) 3-Z-[1-(4-(piperazin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-cyano-2-indolinone

(239) 3-Z-[1-(4-(4-methylpiperazin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-cyano-2-indolinone

(240) 3-Z-[1-(4-(N-benzyl-methylamino-methyl)-anilino)-1-phenyl-methylene]-5-cyano-2-indolinone

(241) 3-Z-[1-(4-(N-(4-chlorobenzyl)-methylamino-methyl)-anilino)-1-phenyl-methylene]-5-cyano-2-indolinone

(242) 3-Z-[1-(4-(N-(3,4-dimethoxybenzyl)-methylamino-methyl)-anilino)-1-phenyl-methylene]-5-cyano-2-indolinone

(243) 3-Z-[1-(4-(7,8-dimethoxy-2,3,4,5-tetrahydro-benz[d]azepin-3-yl-methyl)-anilino)-1-phenyl-methylene]-5-cyano-2-indolinone

(244) 3-Z-[1-(4-chloroanilino)-1-phenyl-methylene]-5-cyano-2-indolinone

(245) 3-Z-[1-(4-bromoanilino)-1-phenyl-methylene]-5-cyano-2-indolinone

(246) 3-Z-(1-anilino-1-phenyl-methylene)-5-cyano-2-indolinone

(247) 3-Z-[1-((4-(pyrrolidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone

(248) 3-Z-[1-((4-(pyrrolidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-(pyridin-3-yl-aminosulphonyl)-2-indolinone

(249) 3-Z-[1-((4-(pyrrolidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-(3-nitro-phenyl-aminosulphonyl)-2-indolinone

Example 4

Dry ampoule containing 75 mg of active substance per 10 ml

Composition:

Active substance	75.0 mg
Mannitol	50.0 mg
water for injections	ad 10.0 ml

Preparation:
Active substance and mannitol are dissolved in water. After packaging the solution is freeze-dried. To produce the solution ready for use, the product is dissolved in water for injections.

Example 5

Dry ampoule containing 35 mg of active substance per 2 ml

Composition:

Active substance	35.0 mg
Mannitol	100.0 mg
water for injections	ad 2.0 ml

Preparation:
Active substance and mannitol are dissolved in water. After packaging, the solution is freeze-dried.

To produce the solution ready for use, the product is dissolved in water for injections.

Example 6

Tablet containing 50 mg of active substance

Composition:

(1) Active substance	50.0 mg
(2) Lactose	98.0 mg
(3) Maize starch	50.0 mg
(4) Polyvinylpyrrolidone	15.0 mg
(5) Magnesium stearate	2.0 mg
	215.0 mg

Preparation:

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side. Diameter of the tablets: 9 mm.

Example 7

Tablet containing 350 mg of active substance

Composition:

(1) Active substance	350.0 mg
(2) Lactose	136.0 mg
(3) Maize starch	80.0 mg
(4) Polyvinylpyrrolidone	30.0 mg
(5) Magnesium stearate	4.0 mg
	600.0 mg

Preparation:

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side. Diameter of the tablets: 12 mm.

Example 8

Capsules containing 50 mg of active substance

Composition:

(1) Active substance	50.0 mg
(2) Dried maize starch	58.0 mg
(3) Powdered lactose	50.0 mg
(4) Magnesium stearate	2.0 mg
	160.0 mg

Preparation:
(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.

This powder mixture is packed into size 3 hard gelatine capsules in a capsule filling machine.

Example 9

Capsules containing 350 mg of active substance

Composition:

(1) Active substance	350.0 mg
(2) Dried maize starch	46.0 mg
(3) Powdered lactose	30.0 mg
(4) Magnesium stearate	4.0 mg
	430.0 mg

Preparation:
(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.

This powder mixture is packed into size 0 hard gelatine capsules in a capsule filling machine.

Example 10

Suppositories containing 100 mg of active substance

1 suppository contains:

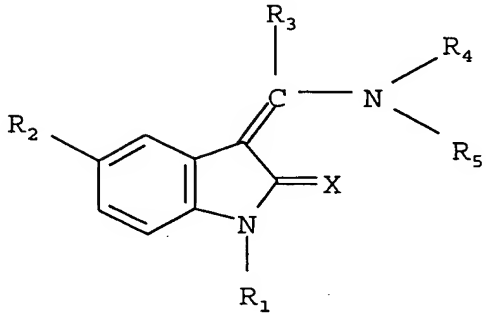
Active substance	100.0 mg
Polyethyleneglycol (M.W. 1500)	600.0 mg
Polyethyleneglycol (M.W. 6000)	460.0 mg
Polyethylenesorbitan monostearate	840.0 mg
	2,000.0 mg

Preparation:

The polyethyleneglycol is melted together with polyethylene sorbitan monostearate. At 40°C the ground active substance is homogeneously dispersed in the melt. It is cooled to 38°C and poured into slightly chilled suppository moulds.

Patent Claims

1. Indolinones substituted in the 5 position of general formula



(I),

wherein

X denotes an oxygen or sulphur atom,

R_1 denotes a hydrogen atom or a prodrug group,

R_2 denotes a hydroxy, C_{1-3}-alkoxy, aryloxy, phenyl-C_{1-3}-alkoxy, cyano, $(HO)_2PO$, $(HO)(C_{1-4}\text{-alkoxy})PO$, $(HO)(\text{aryloxy})PO$, $(HO)(\text{benzyloxy})PO$, $(C_{1-4}\text{-alkoxy})_2PO$, $(\text{aryloxy})_2PO$, $(\text{benzyloxy})_2PO$, $(C_{1-3}\text{-alkylenedioxy})PO$, $H(C_{1-4}\text{-alkoxy})PO$, $H(\text{aryloxy})PO$, $H(\text{benzyloxy})PO$, mercapto, C_{1-3}-alkylmercapto, aryl-mercapto, phenyl-C_{1-3}-alkylmercapto, C_{1-3}-alkylsulphinyl, aryl-sulphinyl, phenyl-C_{1-3}-alkylsulphinyl, C_{1-3}-alkylsulphonyl, aryl-sulphonyl, phenyl-C_{1-3}-alkylsulphonyl, sulpho, C_{1-3}-alkoxysulphonyl, aryloxysulphonyl, phenyl-C_{1-3}-alkoxysulphonyl, amino-sulphonyl, C_{1-4}-alkylaminosulphonyl, arylaminosulphonyl, heteroarylaminosulphonyl, phenyl-C_{1-3}-alkylaminosulphonyl, di-(C_{1-4}-alkyl)-aminosulphonyl, di-(aryl)-aminosulphonyl, di-(phenyl-C_{1-3}-alkyl)-aminosulphonyl, N-(C_{1-3}-alkyl)-arylaminosulphonyl, N-(C_{1-3}-alkyl)-heteroarylaminosulphonyl,

N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylaminosulphonyl or a 4- to 7-membered cycloalkyleneiminosulphonyl group,

R_3 denotes a hydrogen atom, a C_{1-6}-alkyl, C_{3-7}-cycloalkyl, trifluoromethyl or heteroaryl group,

a phenyl or naphthyl group, a phenyl or naphthyl group mono- or disubstituted by a fluorine, chlorine, bromine or iodine atom or by a trifluoromethyl, C_{1-3}-alkyl or C_{1-3}-alkoxy group, whilst in the event of disubstitution the substituents may be identical or different and wherein the abovementioned unsubstituted, mono- and disubstituted phenyl- and naphthyl groups may additionally be substituted

by a hydroxy, hydroxy-C_{1-3}-alkyl or C_{1-3}-alkoxy-C_{1-3}-alkyl group,

by a cyano, cyano-C_{1-3}-alkyl, cyano-C_{2-3}-alkenyl, cyano-C_{2-3}-alkynyl, carboxy, carboxy-C_{1-3}-alkyl, carboxy-C_{2-3}-alkenyl, carboxy-C_{2-3}-alkynyl, C_{1-3}-alkoxycarbonyl, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkyl, C_{1-3}-alkoxycarbonyl-C_{2-3}-alkenyl or C_{1-3}-alkoxycarbonyl-C_{2-3}-alkynyl group,

by a C_{1-3}-alkylcarbonyl, C_{1-3}-alkylcarbonyl-C_{1-3}-alkyl, C_{1-3}-alkylcarbonyl-C_{2-3}-alkenyl or C_{1-3}-alkylcarbonyl-C_{2-3}-alkynyl group,

by an aminocarbonyl, aminocarbonyl-C_{1-3}-alkyl, aminocarbonyl-C_{2-3}-alkenyl, aminocarbonyl-C_{2-3}-alkynyl, C_{1-3}-alkylaminocarbonyl, C_{1-3}-alkylaminocarbonyl-C_{1-3}-alkyl, C_{1-3}-alkylaminocarbonyl-C_{2-3}-alkenyl, C_{1-3}-alkylaminocarbonyl-C_{2-3}-alkynyl, di-(C_{1-3}-alkyl)-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl-C_{1-3}-alkyl, di-(C_{1-3}-alkyl)-aminocarbonyl-C_{2-3}-alkenyl or di-(C_{1-3}-alkyl)-aminocarbonyl-C_{2-3}-alkynyl group,

by a nitro, nitro-C_{1-3}-alkyl, nitro-C_{2-3}-alkenyl or nitro-C_{2-3}-alkynyl group,

by an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl group,

by a C_{1-3}-alkylcarbonylamino, C_{1-3}-alkylcarbonylamino-C_{1-3}-alkyl, N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino-C_{1-3}-alkyl group,

by a C_{1-3}-alkylsulphonylamino, C_{1-3}-alkylsulphonylamino-C_{1-3}-alkyl, N-(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino-C_{1-3}-alkyl group,

by a C_{1-3}-alkylaminosulphonyl, C_{1-3}-alkylaminosulphonyl-C_{1-3}-alkyl, N-(C_{1-3}-alkyl)-C_{1-3}-alkylaminosulphonyl or N-(C_{1-3}-alkyl)-C_{1-3}-alkylaminosulphonyl-C_{1-3}-alkyl group,

by a cycloalkyleneimino, cycloalkyleneiminocarbonyl, cycloalkyleneiminosulphonyl, cycloalkyleneimino-C_{1-3}-alkyl, cycloalkyleneiminocarbonyl-C_{1-3}-alkyl or cycloalkyleneiminosulphonyl-C_{1-3}-alkyl group having 4 to 7 ring members in each case, wherein in each case the methylene group in the 4 position in a 6- or 7-membered cycloalkyleneimino group may be replaced by an oxygen or sulphur atom or by a sulphinyl, sulphonyl, -NH or -N(C_{1-3}-alkyl) group,

or by a heteroaryl or heteroaryl-C_{1-3}-alkyl group,

R_4 denotes a phenyl group,

a phenyl group substituted by a fluorine, chlorine, bromine or iodine atom, by a cyano, nitro, C_{1-3}-alkyl or trifluoromethyl group, by a C_{1-3}-alkoxy group optionally substituted by 1 to 3 fluorine atoms, by an amino-C_{2-3}-alkoxy, C_{1-3}-alkylamino-

C_{2-3}-alkoxy, di-(C_{1-3}-alkyl)-amino-C_{2-3}-alkoxy or benzyl-amino-C_{2-3}-alkoxy group, by a cycloalkyleneimino-C_{2-3}-alkoxy group having 4 to 7 ring members, by a C_{1-3}-alkylmercapto, carboxy, C_{1-3}-alkoxycarbonyl, tetrazolyl or heteroaryl group,

a phenyl group substituted by a 4- to 7-membered cycloalkyleneimino group, wherein

a methylene group linked to the imino group may be replaced by a carbonyl or sulphonyl group or

the cycloalkylene moiety may be fused with a phenyl ring or

one or two hydrogen atoms may each be replaced by a C_{1-3}-alkyl group and/or

in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be substituted by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-C_{1-3}-alkylamino or N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH, -N(C_{1-3}-alkyl), -N(phenyl), -N(C_{1-3}-alkyl-carbonyl) or -N(benzoyl) group,

a C_{1-4}-alkylphenyl group which may be substituted in the alkyl moiety

by an amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, N-(phenyl-C_{1-4}-alkyl)-C_{1-4}-alkylamino, ω-hydroxy-C_{2-4}-alkyl-amino, di-(ω-hydroxy-C_{2-4}-alkyl)-amino or C_{3-7}-cycloalkyl-amino group,

by a 4- to 7-membered cycloalkyleneimino group, wherein

a methylene group linked to the imino group may be replaced by a carbonyl or sulphonyl group or

the cycloalkylene moiety may be fused to a phenyl group or to an oxazolo, imidazolo, thiazolo, pyridino, pyrazino or pyrimidino group optionally substituted by a fluorine, chlorine, bromine or iodine atom, by a nitro, C_{1-3}-alkyl, C_{1-3}-alkoxy or amino group or

one or two hydrogen atoms may each be replaced by a C_{1-3}-alkyl, C_{5-7}-cycloalkyl or phenyl group and/or

in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be substituted by a hydroxy, carboxy, C_{1-4}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-C_{1-3}-alkylamino or N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH, -N(C_{1-3}-alkyl), -N(phenyl), -N(C_{1-3}-alkyl-carbonyl) or -N(benzoyl) group,

by a 5- to 7-membered cycloalkenyleneimino group, wherein the double bond is isolated from the nitrogen atom, by a phenylamino, N-(C_{1-3}-alkyl)-phenylamino, phenyl-C_{1-3}-alkylamino, N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino or di-(phenyl-C_{1-3}-alkyl)-amino group,

by a hydroxy, C_{1-3}-alkoxy, tetrazolyl, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, C_{1-3}-alkylcarbonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino group or by a 4- to 7-membered cycloalkyleneiminocarbonyl group,

a phenyl group substituted by the group of formula

$$-N(R_a)-CO-(CH_2)_n-R_b \qquad (II),$$

wherein

R_a denotes a hydrogen atom or a C_{1-3}-alkyl group,

n denotes one of the numbers 0, 1, 2 or 3 and

R_b denotes an amino, C_{1-4}-alkylamino, phenylamino, N-(C_{1-4}-alkyl)-phenylamino, benzylamino, N-(C_{1-4}-alkyl)-benzylamino or di-(C_{1-4}-alkyl)-amino group, a 4- to 7-membered cycloalkyleneimino group, wherein in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH, -N(C_{1-3}-alkyl), -N(phenyl), -N(C_{1-3}-alkyl-carbonyl) or -N(benzoyl) group, or, if n denotes one of the numbers 1, 2 or 3, it may also denote a hydrogen atom,

or a phenyl group substituted by the group of formula

$$-N(R_c)-(CH_2)_m-(CO)_o-R_d \qquad (III),$$

wherein

R_c denotes a hydrogen atom, a C_{1-3}-alkyl group, a C_{1-3}-alkylcarbonyl, arylcarbonyl, phenyl-C_{1-3}-alkylcarbonyl, C_{1-3}-alkylsulphonyl, arylsulphonyl or phenyl-C_{1-3}-alkyl-sulphonyl group,

m denotes one of the numbers 1, 2, 3 or 4,

o denotes one of the numbers 0 or 1 and

R_d denotes an amino, C_{1-4}-alkylamino, phenylamino, N-(C_{1-4}-alkyl)-phenylamino, benzylamino, N-(C_{1-4}-alkyl)-benzylamino or di-(C_{1-4}-alkyl)-amino group, a

4- to 7-membered cycloalkyleneimino group, wherein the cycloalkylene moiety may be fused to a phenyl ring or in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH, -N(C_{1-3}-alkyl), -N(phenyl), -N(C_{1-3}-alkyl-carbonyl) or -N(benzoyl) group, a C_{1-3}-alkoxy group or a di-(C_{1-4}-alkyl)-amino-C_{1-3}-alkylamino group optionally substituted in the 1 position by a C_{1-3}-alkyl group,

or else, if R_3 does not denote a hydrogen atom, a C_{1-6}-alkyl, C_{3-7}-cycloalkyl or trifluoromethyl group, it may also denote an arylsulphonylaminophenyl or N-(C_{1-3}-alkyl)-arylsulphonylaminophenyl group,

wherein all the single-bonded or fused-on phenyl groups contained in the groups specified under R_4 may be mono- or disubstituted by fluorine, chlorine, bromine or iodine atoms, by C_{1-5}-alkyl, trifluoromethyl, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminosulphonyl, nitro or cyano groups, wherein the substituents may be identical or different, or two adjacent hydrogen atoms of the phenyl groups may be replaced by a methylenedioxy group,

and

R_5 denotes a hydrogen atom or a C_{1-3}-alkyl group,

wherein additionally any carboxy, amino or imino group present may be substituted by a group which can be cleaved *in vivo*,

furthermore the term an aryl group denotes a phenyl or naphthyl group optionally mono- or disubstituted by a fluorine, chlorine or bromine atom or by a trifluoromethyl, C_{1-3}-alkyl, C_{1-3}-alkoxy or nitro group, and

by a heteroaryl group is meant a monocyclic 5- or 6-membered heteroaryl group optionally substituted by a C_{1-3}-alkyl group, whilst the 6-membered heteroaryl group contains one, two or three nitrogen atoms and the 5-membered heteroaryl group contains an imino group optionally substituted by a C_{1-3}-alkyl group, an oxygen or sulphur atom or an imino group optionally substituted by a C_{1-3}-alkyl group and an oxygen or sulphur atom or one or two nitrogen atoms, and moreover a phenyl ring may be fused to the abovementioned monocyclic heterocyclic groups via two adjacent carbon atoms,

the isomers and the salts thereof.

2. Indolinones of general formula I according to claim 1, wherein

X denotes an oxygen atom,

R_1 denotes a hydrogen atom, a C_{1-4}-alkoxycarbonyl or C_{2-4}-alkanoyl group,

R_2 denotes a C_{1-3}-alkoxy, C_{1-3}-alkylmercapto, C_{1-3}-alkylsulphinyl, C_{1-3}-alkylsulphonyl, cyano, $(C_{1-4}\text{-alkoxy})_2PO$, $(C_{1-3}\text{-alkylenedioxy})PO$, aminosulphonyl, C_{1-4}-alkylaminosulphonyl, di-$(C_{1-4}$-alkyl)-aminosulphonyl, phenylaminosulphonyl, N-$(C_{1-3}$-alkyl)-phenylaminosulphonyl, pyridylaminosulphonyl or N-$(C_{1-3}$-alkyl)-pyridylaminosulphonyl group, wherein the phenyl groups contained in the abovementioned groups may be mono- or disubstituted by fluorine, chlorine or bromine atoms, by C_{1-3}-alkyl, trifluoromethyl, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminosulphonyl, nitro or cyano groups, wherein the substituents may be identical or different,

R_3 denotes a phenyl or naphthyl group,

a phenyl or naphthyl group substituted by a fluorine, chlorine, bromine or iodine atom, by a C_{1-3}-alkyl,

trifluoromethyl, hydroxy, C_{1-3}-alkoxy, nitro, cyano, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{1-3}-alkylcarbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino, C_{1-3}-alkylcarbonyl, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group,

R_4 denotes a phenyl group,

a phenyl group substituted by a fluorine, chlorine, bromine or iodine atom, by a cyano, nitro, C_{1-3}-alkyl, trifluoromethyl, C_{1-3}-alkoxy, di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkoxy, C_{1-3}-alkylmercapto, carboxy, C_{1-3}-alkoxycarbonyl, pyrrolyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl group,

a phenyl group substituted by a 5- to 7-membered cycloalkyleneimino group, wherein

a methylene group linked to the imino group may be replaced by a carbonyl or sulphonyl group or

the cycloalkylene moiety may be fused with a phenyl ring or

one or two hydrogen atoms may be replaced in each case by a C_{1-3}-alkyl group and/or

in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be substituted by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH or -N(C_{1-3}-alkyl) group,

a C_{1-4}-n-alkylphenyl group which may be terminally substituted in the alkyl moiety

by an amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, N-(phenyl-C_{1-2}-alkyl)-C_{1-4}-alkylamino, 2-hydroxyethyl-amino, di-(2-hydroxyethyl)-amino or C_{5-6}-cycloalkylamino group,

by a 5- to 7-membered cycloalkyleneimino group, wherein

one or two hydrogen atoms may each be replaced by a C_{1-3}-alkyl group or

the methylene group in the 4 position of a piperidino group may be substituted by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group or

the cycloalkylene moiety may be fused to a phenyl group or to an imidazolo or pyridino group optionally substituted by a fluorine, chlorine or bromine atom, by a C_{1-3}-alkyl or C_{1-3}-alkoxy group, or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH or -N(C_{1-3}-alkyl) group,

by a 3-pyrrolin-1-yl or 3,4-dehydropiperidino group, by a phenylamino, N-(C_{1-3}-alkyl)-phenylamino, phenyl-C_{1-3}-alkylamino, N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkyl-amino or di-(phenyl-C_{1-3}-alkyl)-amino group,

by an aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, C_{1-3}-alkylcarbonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino group,

a phenyl group substituted by the group of formula

$$-N(R_a)-CO-(CH_2)_n-R_b \qquad (II),$$

wherein

R_a denotes a hydrogen atom or a C_{1-3}-alkyl group,

n denotes one of the numbers 0, 1 or 2 and

R_b denotes an amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, phenylamino or benzylamino group or a 5- to 6-membered cycloalkyleneimino group, wherein the methylene group in the 4 position of the piperidino group may be replaced by an oxygen or sulphur atom or by a sulphinyl, sulphonyl, -NH or -N(C_{1-3}-alkyl) group, or, if n denotes the number 1 or 2, may also denote a hydrogen atom,

or a phenyl group substituted by the group of formula

$$-N(R_c)-(CH_2)_m-(CO)_o-R_d \qquad (III),$$

wherein

R_c denotes a hydrogen atom, a C_{1-3}-alkyl, C_{1-3}-alkylcarbonyl or C_{1-3}-alkylsulphonyl group,

m denotes one of the numbers 1, 2 or 3,

o denotes one of the numbers 0 or 1 and

R_d denotes an amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, phenylamino or benzylamino group or a 5- to 6-membered cycloalkyleneimino group, wherein the methylene group in the 4 position of the piperidino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH or -N(C_{1-3}-alkyl) group, a di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl-amino group optionally substituted in the 1 position by a C_{1-3}-alkyl group or, if n denotes the number 1 or 2, it may also denote a hydrogen atom,

wherein all the single-bonded or fused-on phenyl groups contained in the groups mentioned under R_4 may be mono- or disubstituted by fluorine, chlorine or bromine atoms; by C_{1-3}-alkyl, trifluoromethyl, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminosulphonyl, nitro or cyano groups, wherein the substituents may be identical or different, or two adjacent hydrogen atoms of the phenyl groups may be replaced by a methylenedioxy group, and

R_5 denotes a hydrogen atom or a methyl group,

the isomers and the salts thereof.

3. Indolinones of general formula I according to claim 1, wherein

X denotes an oxygen atom,

R_1 denotes a hydrogen atom, a C_{1-4}-alkoxycarbonyl or C_{2-4}-alkanoyl group,

R_2 denotes a C_{1-3}-alkoxy, C_{1-3}-alkylmercapto, C_{1-3}-alkylsulphinyl, C_{1-3}-alkylsulphonyl, cyano, $(C_{1-4}\text{-alkoxy})_2PO$, aminosulphonyl, C_{1-4}-alkylaminosulphonyl, di-$(C_{1-4}$-alkyl)-aminosulphonyl, phenylaminosulphonyl, N-$(C_{1-3}$-alkyl)-phenylaminosulphonyl, 3-pyridylaminosulphonyl or N-$(C_{1-3}$-alkyl)-3-pyridylaminosulphonyl group, wherein the phenyl groups contained in the abovementioned groups may be substituted by a fluorine, chlorine or bromine atom or by a C_{1-3}-alkyl, trifluoromethyl, C_{1-3}-alkoxy, nitro or cyano group,

R_3 denotes a phenyl or naphthyl group, but particularly the phenyl group,

R_4 denotes a phenyl group,

a phenyl group substituted by a fluorine, chlorine, bromine or iodine atom, by a cyano, nitro, C_{1-3}-alkyl, trifluoromethyl, C_{1-3}-alkoxy, di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkoxy, C_{1-3}-alkylmercapto, carboxy, C_{1-3}-alkoxycarbonyl, pyridinyl or imidazolyl group,

a phenyl group substituted by a pyrrolidino, piperidino, 2,6-dimethyl-piperidino, 3,5-dimethyl-piperidino or azepino group, wherein

the methylene group in the 4 position of the piperidino group may be substituted by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH or -N(C_{1-3}-alkyl) group,

a C_{1-3}-n-alkylphenyl group which may be terminally substituted in the alkyl moiety

by an amino, C_{1-4}-alkylamino or di-(C_{1-4}-alkyl)-amino group,

by a N-(phenylmethyl)-C_{1-4}-alkylamino group which may be monosubstituted in the phenyl moiety by a fluorine, chlorine or bromine atom or by a C_{1-3}-alkyl, C_{1-3}-alkoxy, trifluoromethyl or cyano group, or disubstituted by two C_{1-3}-alkyl or C_{1-3}-alkoxy groups,

by a 2-hydroxyethyl-amino, di-(2-hydroxyethyl)-amino, cyclopentylamino or cyclohexylamino group,

by a pyrrolidino, piperidino, 2,6-dimethyl-piperidino, 3,5-dimethyl-piperidino or cyclohexyleneimino group, wherein

the methylene group in the 4 position of the piperidino group may be substituted by a carboxy,

C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group or

may be replaced by an oxygen or sulphur atom or by a sulphinyl, sulphonyl, -NH or -N(C_{1-3}-alkyl) group,

or the cycloalkylene moiety may be fused to a phenyl group,

by a 3-pyrrolin-1-yl or 3,4-dehydropiperidino group, by a phenylamino, N-(C_{1-3}-alkyl)-phenylamino, phenyl-C_{1-3}-alkylamino, N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino or di-(phenyl-C_{1-3}-alkyl)-amino group,

by an aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, C_{1-3}-alkylcarbonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino group,

a phenyl group substituted by the group of formula

$$-N(R_a)-CO-(CH_2)_n-R_b \qquad (II),$$

wherein

R_a denotes a C_{1-3}-alkyl group,

n denotes one of the numbers 0, 1 or 2 and

R_b denotes an amino, C_{1-3}-alkylamino, di-(C_{1-4}-alkyl)-amino, pyrrolidino or piperidino group, wherein the methylene group in the 4 position of the piperidino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH or -N(C_{1-3}-alkyl) group,

or a phenyl group substituted by the group of formula

$$-N(R_c)-(CH_2)_m-(CO)_o-R_d \qquad (III),$$

wherein

R_c denotes a C_{1-3}-alkylcarbonyl or C_{1-3}-alkylsulphonyl group,

m denotes one of the numbers 1, 2 or 3,

o denotes one of the numbers 0 or 1 and

R_d denotes an amino, C_{1-3}-alkylamino, di-(C_{1-4}-alkyl)-amino, pyrrolidino or piperidino group, wherein the methylene group in the 4 position of the piperidino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH or -N(C_{1-3}-alkyl) group, or a di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkylamino group optionally substituted in the 1 position by a C_{1-3}-alkyl group,

or a phenylsulphonylaminophenyl or N-(C_{1-3}-alkyl)-phenyl-sulphonylaminophenyl group,

wherein all the single-bonded or fused-on phenyl groups contained in the groups mentioned under R_4 may be substituted by a fluorine, chlorine or bromine atom, by a methyl, trifluoromethyl, methoxy, carboxy, methoxy-carbonyl, ethoxycarbonyl, aminosulphonyl, nitro or cyano group or two adjacent hydrogen atoms of the phenyl groups may be replaced by methoxy groups or by a methylenedioxy group, and

R_5 denotes a hydrogen atom,

the isomers and the salts thereof.

4. The following substituted indolinones of general formula I according to claim 1:

(a) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-methylsulphinyl-2-indolinone,

(b) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-methylsulphonyl-2-indolinone,

(c) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-(N-methyl-N-phenyl-aminosulphonyl)-2-indolinone,

(d) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-(N-butyl-N-methyl-aminosulphonyl)-2-indolinone,

(e) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-(phenylaminosulphonyl)-2-indolinone,

(f) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone,

(g) 3-Z-[1-(4-((N-benzyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone,

(h) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone,

(i) 3-Z-[1-(4-(N-(dimethylaminocarbonyl-methyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone,

(j) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-5-diethoxyphosphoryl-2-indolinone,

(k) 3-Z-[1-(4-(2-dimethylamino-ethyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone,

(l) 3-Z-[1-(4-(dimethylamino-methyl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone,

(m) 3-Z-[1-(4-(N-methyl-acetylamino)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone and

(n) 3-Z-[1-(4-(N-methyl-piperazin-1-yl)-anilino)-1-phenyl-methylene]-5-(phenyl-aminosulphonyl)-2-indolinone,

the isomers and the salts thereof.

5. Physiologically acceptable salts of the compounds according to claims 1 to 4.

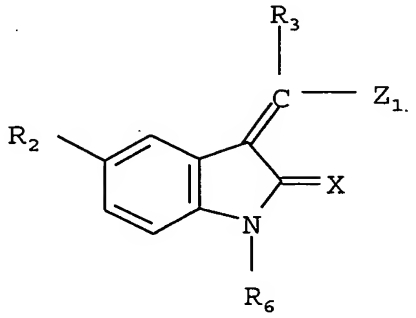
6. Pharmaceutical compositions containing a compound according to at least one of claims 1 to 4 or a salt according to claim 5 optionally together with one or more inert carriers and/or diluents.

7. Use of a compound according to at least one of claims 1 to 4 or a salt according to claim 5 for preparing a pharmaceutical composition which is suitable for treating excessive or anomalous cell proliferation.

8. Process for preparing a pharmaceutical composition according to claim 6, characterised in that a compound according to at least one of claims 1 to 4 or a salt according to claim 5 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

9. Process for preparing the compounds according to claims 1 to 5, characterised in that

a. a compound of general formula

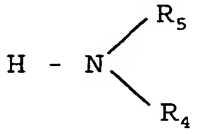


(IV),

wherein
X, R_2 and R_3 are defined as in claims 1 to 4 and
R_6 denotes a hydrogen atom, a protecting group for the nitrogen atom of the lactam group or a bond to a solid phase and

Z_1 denotes a halogen atom, a hydroxy, alkoxy or aryloxy group,

is reacted with an amine of general formula

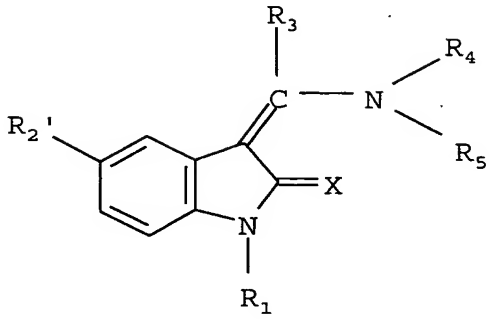


(III),

wherein
R_4 and R_5 are defined as in claims 1 to 4, and if necessary any protecting group used for the nitrogen atom of the lactam group is cleaved or a compound thus obtained is cleaved from a solid phase or

b. in order to prepare a compound of general formula I wherein R_2 denotes one of the substituted sulphinyl or sulphonyl groups mentioned hereinbefore,

a compound of general formula



(VI),

wherein
R_1 and R_3 to R_5 are defined as in claims 1 to 4 and
R_2' denotes one of the substituted mercapto or sulphinyl groups mentioned for R_2 in claims 1 to 4, is oxidised and

subsequently, if desired, a compound of general formula I thus obtained which contains an alkoxycarbonyl group is converted by hydrolysis into a corresponding carboxy compound or

a compound of general formula I thus obtained which contains an amino or alkylamino group is converted by alkylation or reductive alkylation into a corresponding alkylamino, dialkylamino or pyrrolidino compound or

a compound of general formula I thus obtained which contains an amino or alkylamino group is converted by acylation into a corresponding acyl compound or

a compound of general formula I thus obtained which contains a carboxy group is converted by esterification or amidation into a corresponding ester or aminocarbonyl compound or

a compound of general formula I thus obtained which contains a nitro group, is converted by reduction into a corresponding amino compound or

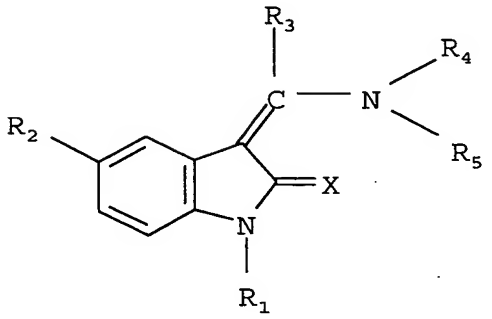
if necessary any protecting group used to protect reactive groups during the reactions is cleaved or

if desired a compound of general formula I thus obtained is subsequently resolved into the stereoisomers thereof or

a compound of general formula I thus obtained is converted into the salts thereof, in particular for pharmaceutical use into the physiologically acceptable salts thereof with an inorganic or organic acid or base.

Abstract

The present invention relates to indolinones of general formula



(I),

substituted in the 5 position
wherein
R_1 to R_5 and X are defined as in claim 1, the isomers and the salts thereof, particularly the physiologically acceptable salts thereof which have valuable pharmacological properties, especially an inhibitory effect on various kinases and cyclin/CDK complexes, on receptor tyrosine kinases as well as on the proliferation of tumour cells, pharmaceutical compositions containing these compounds, their use and processes for preparing them.